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CLINICAL EXPERIENCES WITH THE APPLICATION OF POLYTHENE CELLOPHANE UPON ANEURYSMS OF THE THORACIC VESSELS

OSLER A. ABBOTT, M.D.
ATLANTA, GA.

IT IS important to stress at the outset that this paper deals essentially with the experiences obtained in applying Polythene cellophane to aneurysms of the human intrathoracic vessels. It is far too early in the period of observation which has been allowed to come to any definite conclusions. This paper must be considered in the form of a preliminary report. In view of certain rather dramatic findings noted upon the experimental application of cellophane upon the vessels of animals, I felt that one was justified in applying this method to a fairly large group of human patients who present themselves with a disease which entails such a serious prognosis as a large aneurysm of an intrathoracic vessel. The application of this material to the human aorta is certainly not an original procedure, but this communication will report the application of this material to portions of certain vessels which have not previously been so dealt with, and describes a larger group of patients so treated than elsewhere reported.

It is important for us to refresh our memories in regard to the clinical history of an aortic aneurysm. The life expectancy of a patient with an aneurysm of the aorta is an extremely variable matter, ranging from the patient in whom a fatal result occurs in a period of less than six months after the first x-ray evidence of aneurysmal disease is obtained to the other extreme of the patient in whom an aneurysm may be observed to be present over a period of from ten to twenty years.

Aneurysms of the thoracic vessels may differ greatly in their etiology. Aneurysms with the same etiology may vary greatly in their life expectancy. These considerations, therefore, make one realize that only a study of a very large group of patients having aneurysmal disease from all known causes, and followed over a period of many years, can allow us to make any definitive conclusions.

From the Emory University School of Medicine, Department of Surgery (Thoracic).

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There is no doubt that the final method of control of aneurysmal disease is the prevention of its cause. However, it does seem reasonable to consider that once an aneurysm has been produced, there is a permanent structural defect, which will need structural correction. The direct approach upon a structural defect, so as to re-mold a facsimile of the normal, is the ideal of surgery. With present-day limitations it is not always possible for one to satisfy this ideal. When one is confronted with a lesion of a nonsacrificiable vessel it is often necessary to approach the problem by "second-best" methods.

In summary, then, the modes of attack upon aneurysmal disease of a thoracic structure consist, per primam, of a reconstitution of the normal tube for the passage of blood. The "second-best" type of methods have had to be applied to the thoracic aorta during recent years and consist, essentially, of four modes of attack: (1) the repair of the wall of the aneurysm by internal plication, reconstituting a tube of normal caliber but allowing diseased walls to remain; (2) the promotion of a thick layer of blood clot within the aneurysm, in order to increase the protective character of the wall and thus reinforce the weakened area; (3) progressive obliteration of the aneurysmal sac by means of the promotion of periarterial fibroblastic reaction; (4) any combination of the preceding three types of procedure. It would seem reasonable to assume that a combination of any, or all, of the three indirect methods of approach would constitute the best method to substitute for direct and satisfactory reconstruction.

The method utilized in this study has relied upon the formation of a chronic, progressive, constrictive, periarterial, fibroblastic reaction in the hope of ultimate obliteration of the aneurysmal cavity, or at least sufficient strengthening of the wall to eliminate the threat of fatal rupture. In the latter period of the study we have added attempts to increase the thickening of the inner wall of the aneurysm along with the attack upon the outer wall. Polythene cellophane is undoubtedly only the forerunner of future preferable substances to produce periarterial fibroblastic reaction. Pearse,[1] in 1940, published studies upon the constrictive effect of the application of cellophane upon the aorta of dogs. His interest in cellophane arose, originally, with the work of Page,[2] in the application of this substance about the kidney in the promotion of experimental hypertension. This latter author noted "a marked tissue reaction within three to five days following the application of this substance. A constricting, dense, fibroblastic, collagenous formation about the surface of the kidney, varying from 3 to 5 mm. in thickness, was noted to be present within two weeks."

It was in 1941 that Harper and Robinson[3] reported a most interesting clinical application of this substance, namely, the use of cellophane about a ligated ductus arteriosus in which there was evidence of recanalization two weeks following the original operative procedure. At the original procedure, cellophane had been applied and the subsequent obliteration of the channel two months later was felt to be evidence that the reaction incited by the surrounding cellophane had contributed to the closure of this channel.

In 1943 two missionaries in Arabia, Harrison and Chandy,[4] utilized cellophane about aneurysms of the axillary artery in two patients. In the first patient there was evidence of obliteration of the lumen of this vessel in approximately

nine months, while intervening secondary infection in the second patient necessitated secondary high ligation of the vessel and excluded the case from any satisfactory conclusions.

The irritating factors of cellophane have been the cause of considerable discussion among many workers. Some have used this material for the prevention of tissue reaction, while others have employed it with a diametrically opposed purpose. Thus, in contradistinction to the reports of Pearse, Page, Harper and Robertson, Harrison, and Chandy, there is the work of Donati[5] in 1937, and McKeever[6] in 1943, wherein the material was used in the treatment of arthritic lesions, with the hope of resurfacing mobile joints. This confusion led to the very valuable study carried out by Poppe and de Oliveira[7] in regard to the different physiologic properties of varying types of commercial cellophane. A series of animal experiments were conducted, utilizing five different basic types of this material. A very marked fibrous tissue reaction surrounding the section of the aorta in close proximity to Polythene variety of cellophane was constantly noted. Their studies promoted the following conclusions:

> (1) Moisture-resistant cellophane and types 300 P.U.T. 71, and 300 T.T. 62, cause minimal if any reaction. (2) Experimental studies have shown that in order to obtain the desired result it is necessary to use a particular type of cellophane, since some varieties produce no fibrosis. (3) Polythene cellophane has been found useful, not only in the treatment of aortic aneurysms, but also in the obliteration of a patent ductus arteriosus.

I derived my interest in this substance from ideas about the subject expressed by Dr. Evarts A. Graham in 1944. To my knowledge the first instance of the application of this substance to the human aorta was carried out by Graham in 1944.

It would seem well at this time to describe the technical considerations involved in the sterilization and application of this material. The technical name for the type of cellophane used is 1.5 Mil Polythene (NV-7-14).* This material has been sterilized by keeping it in 70 per cent alcohol for twenty-four to forty-eight hours prior to use. Following the exposure of the aneurysmal area of the vessel, plus at least two inches of the vessel above and below the site of disease; this material is applied in from two to four thicknesses so as to surround the diseased area and a one-to-two inch area of apparently normal vessel above and below the aneurysm. It is important to emphasize that the material is laid in contact with the aneurysm, and in no way constricts it. If a direct constricting action were used the danger of rupture of the vessel at the uppermost junction of the cellophane with the vessel would probably occur. The substance is used purely to stimulate a fibroblastic reaction about a diseased area.

Fluid is formed in contact with any foreign body. Therefore, this material may well float away unless definite methods are used to fix it in place. This fixation is carried out by suturing the material to near-by structures and wheresoever the wall appears sufficiently healthy. Fine arterial silk is used to sew the material directly to the vessel wall. Chemotherapeutic agents are utilized

*This material has been provided for experimental use by E. I. Du Pont de Nemours Company, Cellophane Division, Wilmington, Del.

liberally, both before, during, and following the operation in order to prevent infection which is so likely to occur about a foreign body.

To date, this material has been applied in thirty-two separate individuals, and in several of the patients more than one aneurysm has been treated. It has been felt that the application of this material is truly clinical experimentation, and therefore no patient has been subjected to the procedure unless the lesion appeared to be a definite threat to life should no treatment be instituted. This has constituted a very strict test of the material and therefore the final results would in no way be comparable to the application of this substance in considerably less-advanced lesions.

The predominant lesion treated has been aneurysmal disease secondary to syphilitic aortitis. The majority of such patients have been of relatively low economic and mental status, and it has been extremely difficult to maintain a satisfactory follow-up. Furthermore, in such patients wherein a fatal issue occurs, it has frequently been impossible to obtain permission for post-mortem examination. However, this study has not been confined to lesions of syphilitic etiology. Aneurysms of congenital origin, arteriosclerotic origin, and of dissecting type have been treated with cellophane application and their postoperative course observed. During the course of this study several of the individuals presented lesions in a sufficiently advanced state that extreme interference with respiratory function was already present. This allowed certain maneuvers of thoracic decompression to be carried out which were found to be necessary in order to prepare the patient for an open transthoracic procedure.

I have had opportunity to apply this substance to all areas of the thoracic aorta, both intra- and extrapericardial. The substance has also been applied to the innominate and left subclavian arteries and to the pulmonary arteries. Those of us concerned in this study have been impressed with the frequency with which areas of multiple aneurysmal disease are prone to occur in the patient with syphilitic aortitis. It has also been interesting to note the marked frequency with which aneurysmal disease may be present, and on fluoroscopy no pulsation of the presenting mass may be observed. The explanation for this phenomenon is really quite simple, in that on opening the thorax one frequently finds the overlying pleura markedly thickened, and only after the release of this overlying membrane does pulsation appear. In certain instances the lack of pulsation may be due to the degree of thrombosis within the aneurysmal sac. It has been our observation to note that only about 30 per cent of aortic aneurysms will be seen to pulsate in an unequivocal manner on fluoroscopic examination.

It does not seem necessary in a communication of this type to consider in any great detail the diagnostic measures involved in patients with aneurysmal disease. It is of utmost importance to realize that any mass, situated in the region of a vascular channel, has the potential of being aneurysmal in character. Again, it should be emphasized that the lack of pulsation does not in any way preclude the possibility of aneurysm. It has been our experience to note that mediastinal lesions which are associated with partial atelectasis, and especially

if such atelectasis may be bilateral, should make one strongly suspicious of a vascular origin of the mass noted. It is, of course, obvious that there is a definite place for the application of angiocardiographic studies in patients of this type. However, in such patients in whom there is any major degree of bronchial compression, such that wheezes are noted on physical examination, it has been our policy not to carry out angiocardiographic investigation except in rare cases. This has been because of the associated bronchospasm which may occur with angiocardiographic studies and such bronchospasm might constitute an unnecessary and hazardous risk.

No unusual types of visualization of the thoracic aorta have been carried out by means of Diodrast, but rather the study has been confined to injection into the basilic vein. I am cognizant of the studies carried out in which the material is introduced either directly into the aorta or into one of its major tributaries.

In view of the common knowledge of the diffuse character of syphilitic and arteriosclerotic disease of major blood vessels, it has not been felt advisable to instrument directly such an organ as the aorta. The roentgenkymogram has, of course, been of considerable disappointment in view of the fact that it only represents a permanent record of what may be seen with the fluoroscope, and the lack of pulsation under fluoroscopy would lead one to the conclusion which we have also achieved clinically, that the kymogram has been of no real value in the study of such diseases, unless definite pulsation is suspected on fluoroscopy.

It has been interesting to note, with Diodrast intravascular studies, the frequency of multiple aneurysmal disease in patients with syphilitic arteritis. One is, of course, concerned with the possibility of a Herxheimer reaction in association with the lesions of syphilitic etiology. To date, preoperative penicillin therapy has been instituted in such patients, and all have been carried to a minimum of 7 million units as a total including the pre- and postoperative course, in an attempt to treat the underlying etiologic agent. In the patients treated to date, no major serious complication of a Herxheimer type has been noted. The evaluation of the blood pressure in the right and left arm, and in both lower extremities, is a necessary investigative measure in all patients with central mediastinal mass and has been carried out in all patients with aneurysmal disease.

What may one expect to find in follow-up study of an aortic aneurysm which has been treated with cellophane application? It is reasonable to expect an initial enlargement of the shadow. This is, in part, due to a release of overlying constricting pleura and also due to formation of fluid about the foreign body which has been applied. There is no reason, from animal experimentation, to expect any dramatic changes. Actual constriction of the normal aorta of the dog may take three to six months to occur, and when one is dealing with a lesion of the massive size as is being described, one would hardly expect an obliteration of the channel, or even if the channel is constricted to a normal size the resulting wall should be so thickened as still to constitute a major x-ray shadow. An original enlargement of the shadow of the aneurysm has been noted, and then a return to the original dimension.

The next consideration to be dealt with is the matter of actual and potential complications of this surgical maneuver. In certain portions of this study one was treading upon previously unbroken ground. Therefore, it is natural to expect that certain errors, both in judgment and technique, were committed. It is felt in evaluating a new procedure that it is beneficial for us to publicize such errors, in the hope of forestalling its commission by others. In dealing with aneurysmal disease it is important to appreciate the limitations of x-ray investigation. It is common knowledge that an aneurysm pulsating constantly against a firm and rigid structure, such as bone, will undergo a weakening and thinning of this area of wall contact. Therefore, it is important not to unroof

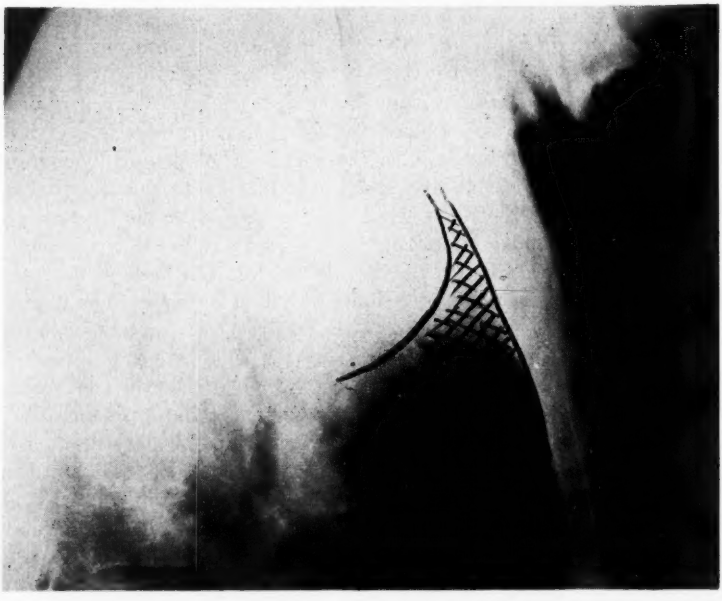


Fig. 1.—Patient, Mr. E. H. Lateral x-ray view to demonstrate lack of opacification when looking tangentially at an aortic aneurysm. Shaded area noted by cross-hatching appears clear, but actually aneurysm was in contact with the sternum throughout this area.

bone overlying an area of direct contact with the area of vascular disease. Great stress has been laid upon the lateral film in an attempt to evaluate the proximity of the aneurysm to bone, especially such structures as the sternum. In at least five patients what appears to be a good clear area has been seen between the aneurysm and the sternum (Fig. 1), and yet upon removing the sternum and leaving the posterior periosteum intact, it is obvious that an extremely thin-walled aneurysm is in direct contact with this periosteum. It is reasonable to feel that an aneurysm of thin wall containing blood would not be expected to present a dense or discrete shadow, especially in such a projection as the lateral film.

In the first two patients (Figs. 2 and 3) presenting massive aneurysm, pressing against the posterior surface of the sternum, there was major com-

Fig. 2.—Patient, Mr. E. H. Photograph illustrating the inclusion of the dressing within stay sutures after the aneurysm illustrated in Fig. 1 ruptured during decompression maneuvers.

Fig. 3.—Patient, G. B. Photograph illustrating a large aneurysm arising from innominate artery and presenting in the clavicular and right cervical region. Aneurysm ruptured spontaneously during decompression through a thinned-out area of its wall pressing against the second rib.

pression of the lower trachea and both main stem bronchi. In attempting to decompress these two lesions, spontaneous rupture of the anterior surface of the aneurysmal wall occurred at the operating table. This catastrophe was dealt with by keeping pressure with the hands over the area of leakage, and sewing a large wide strip of thrombin-soaked Gel-foam to a strip of cellophane, and then placing sutures to near-by structures, so that this lay above the operator's hand; sutures for closure of the wound were placed, following which the hand was removed, the Gel-foam plaque applied immediately to the leaking surface, and the wound closed rapidly. This proved to be a temporizing method in both cases, inasmuch as one patient subsequently ruptured fatally on the sixteenth day, and the other on the nineteenth. At autopsy in the first patient it was found that rupture had occurred at a new site and there was apparent closure of the accidental rupture occurring on the operating table. In the second patient the fatal episode consisted of leakage through the original site of rupture. In both these patients, at the time the accident occurred, the ascending aorta was explored inasmuch as both were lesions of the innominate artery, in the hope that one might be able to ligate the base of the artery. However, in both cases the aneurysmal and syphilitic disease was involved down onto the wall of the ascending aorta in such a manner that no such measure could be undertaken.

The main lesson to be learned from this experience is not to remove bone directly in contact with aneurysmal wall. The second consideration is to appreciate that the lateral projection x-ray may not tell the exact proximity of the aneurysmal wall to such an overlying structure as the sternum.

A second, most interesting, complication of aneurysmal disease was also discovered by the process of trial and error. Many of the colored patients with aneurysmal disease originally enter the hospital due to the pulmonary complications of the aneurysm. Thus, they are admitted to the Medical Service because of pneumonia and atelectasis. In one such patient delayed resolution of the pneumonic process led to further detailed x-ray studies and a proper diagnosis of the underlying obstructive agent. There was a total atelectasis of the left lung, and a major aneurysm of the descending arch of the aorta. The patient had achieved maximum benefit from chemotherapeutic agents and medical therapy, and no major complaints relative to the respiratory function were present. The atelectasis persisted.

The patient was taken to the operating room, anesthesia induced, and endotracheal tube introduced. At the time of induction of the endotracheal tube apnea appeared, which was thought by the anesthetist to be due to depth of anesthesia. The patient was then placed in position for a left posterolateral approach. Despite release from anesthetic agents the patient's apnea persisted, so that he was returned to the supine position and the endotracheal tube removed. It was obvious that the patient was breathing with marked difficulty, as from obstruction. Bronchoscope was introduced and it was very alarming to visualize the severe degree of edema and constriction of the lower end of the trachea, as well as the entire left main stem bronchus, secondary to aneurysmal compression. Despite all attempts at resuscitative measures the patient died about four hours later.

Therefore, it was concluded that any patient having major tracheal or bronchial obstruction, secondary to an aneurysm, has not only compression but severe associated edema due to obstruction of venous flow, and that this obstruction must be corrected prior to any open intrathoracic operative procedures (Fig. 4). Again, by a process of trial and error and referral to previous works on decompression of the thoracic inlet, three major methods for decompression were evolved. This procedure is always carried out under Novocain infiltration and may be assisted by a very slow dilute intravenous drip of sodium pentothal. True general anesthesia is diligently avoided. It seems that with general anesthesia there is some relaxation of the support of the tracheal and bronchial wall which may convert a partial into a total obstruction.

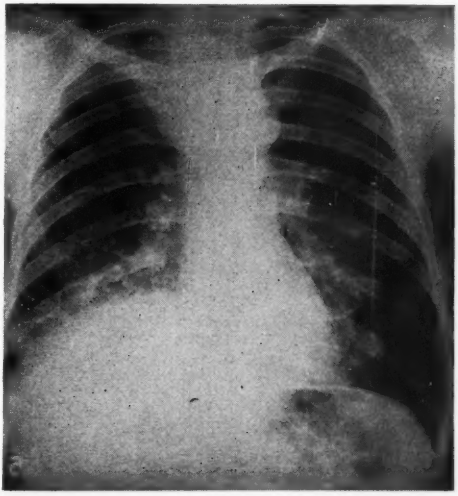


Fig. 4.—Patient, Mr. W. B. This x-ray illustrates the tracheobronchial compression produced by a syphilitic aneurysm of the innominate artery. Note the atelectasis of the right middle and lower lobes and obstructive emphysema of the right upper lobe. This patient withstood intrathoracic surgery well after a preliminary decompression operation on the right side

The measures which we have utilized for decompression are outlined in Figs. 5, 6, and 7 and consist, essentially, of enlarging the thoracic inlet by resection of a portion of the clavicle and upper two ribs over a lesion which is obstructing one bronchus. In some cases it is necessary to do this bilaterally, if both bronchi are involved and the lesion lies against the sternum. In lesions which are well separated from the sternum, such as an aneurysm of the descending portion of the arch or descending thoracic aorta, a sternal split with implantation of supporting wedge material, either of bone or metal, has been utilized. Following this operative procedure the patient frequently notes an almost immediate improvement in respiration. However, a change in x-ray and clinical findings is seldom noted prior to two weeks following operation, and it is often necessary to wait from three to four weeks to obtain maximum clinical benefit. This is

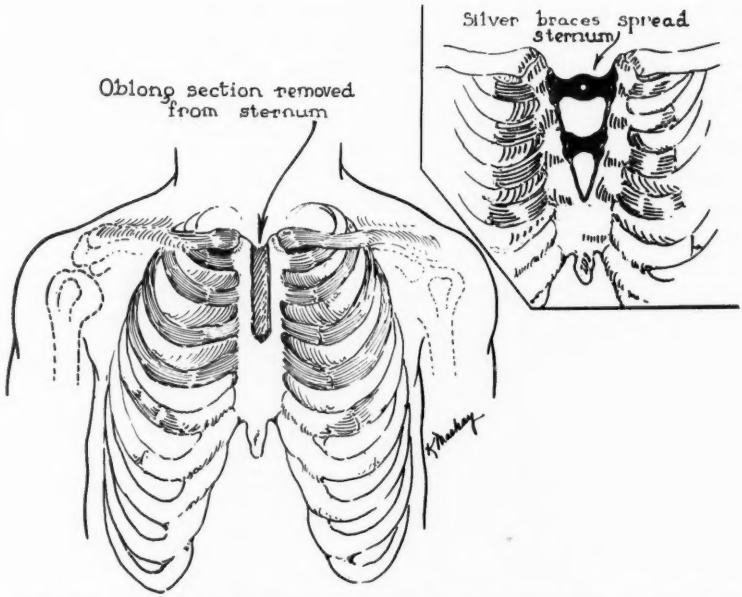


Fig. 5.—Illustration showing method for decompression of thoracic inlet used early in this study. This method was found to be the least effective, as well as the most hazardous.

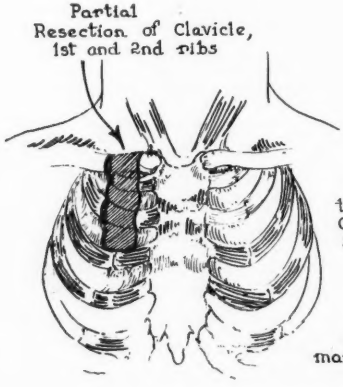


Fig. 6.

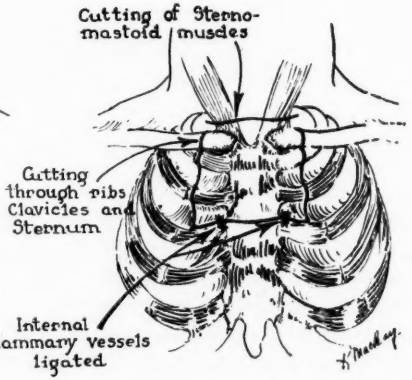


Fig. 7.

Figs. 6 and 7.—These illustrations demonstrate the most satisfactory method for decompression of the thoracic inlet. Fig. 6 demonstrates the amount of bone and periosteum resected at the first stage. Transection of the ligamentous structures behind the clavicle is not illustrated but the desired anterior displacement of the area outlined in Fig. 7 will not occur until these ligaments have been cut. Transection of the sternum is rarely needed and may be dangerous.

due to the time necessary for the resolution of the severe edema present secondary to the aneurysm.

A third complication which was noted to arise in the carrying out of this clinical experimentation has been the effect of irritating cellophane when brought into contact with the auricles. On three occasions the material has been applied within the pericardial sac. Two patients having a primary aneurysm of the ascending aorta were treated by the application of cellophane. The first operation (Fig. 8) was done early in the study, and irritative type cellophane placed about the area of aneurysmal disease. The postoperative course was uneventful, there being no arrhythmias or serious cardiac dysfunction noted. This patient was followed for a period of ten weeks following surgery and had resumed gainful occupation by that time. Unfortunately it has not been possible to obtain any follow-up data in regard to this patient since that time.

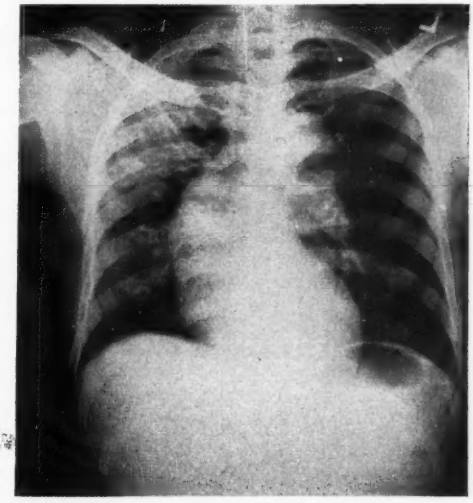


Fig. 8.—X-ray view demonstrating a large aneurysmal dilatation of the lateral wall of the ascending aorta. Note the secondary atelectasis of the right upper lobe as well as the obstructive emphysema of the right middle and lower lobes. Intrapericardial cellophane was applied in this instance.

A second colored patient with aneurysmal disease of the ascending aorta was treated by application of irritative cellophane ten months before this communication. In this patient a second outer layer of nonirritative type of cellophane was applied over the lower third of the ascending aorta in order not to bring irritative cellophane in contact with the auricular appendage. This patient's postoperative course was not complicated by any unusual cardiac arrhythmia. The outer layer of nonirritative type of cellophane was applied in this patient, due to an unfortunate experience gained on the second patient in whom intrapericardial cellophane was applied.

This patient (Figs. 9 and 10) was a 31-year-old white woman, in whom there had been a very rapid and progressive enlargement of a primary aneurysm of the main pulmonary artery. This lesion was treated by the primary application of Polythene cellophane, with no method of protection utilized to prevent contact of the cellophane with the auricles. The patient's postoperative course was uneventful until the eighth day,

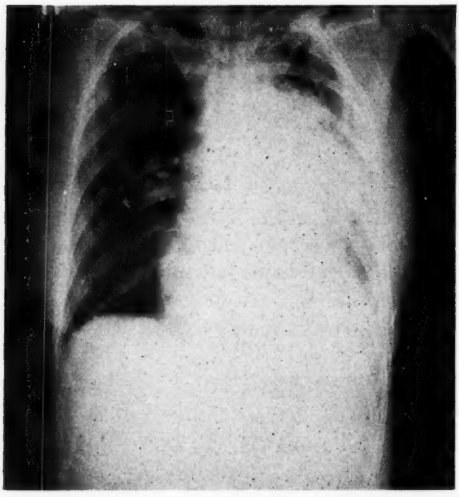


Fig. 9.—Patient, Mrs. R. W. X-ray film demonstrating a massive solitary aneurysm of the main pulmonary artery.

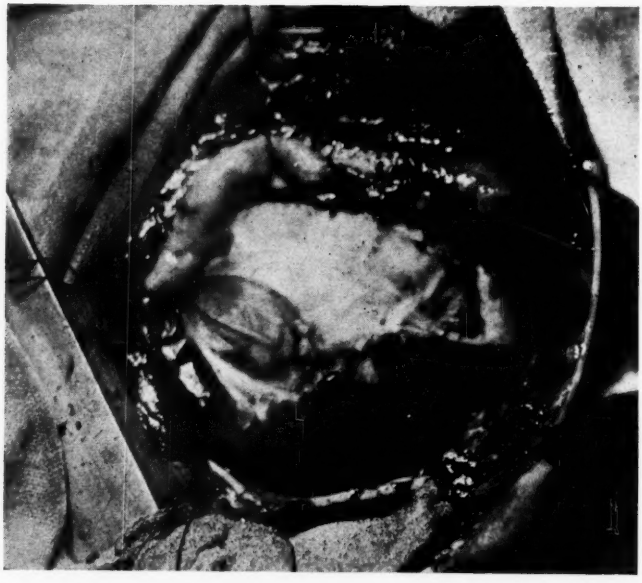


Fig. 10.—Patient, Mrs. R. W. Photograph illustrates the appearance of the lesion at the time of operation. Cellophane was applied within the pericardial sac in this instance without the use of a protective layer of nonreactive cellophane.

postoperatively, when she suddenly developed dyspnea and precordial distress apparently in association with ventricular fibrillation. The patient died very soon after the onset of this episode, so that exact details of the type of arrhythmia which might have been obtained from electrocardiographic studies were not available.

Fig. 11.—Patient, Mrs. R. W. Photograph taken of the postmortem specimen. Note nodular reaction over outer wall of the primary aneurysm of the pulmonary artery. Cellophane had been in place for eight days.

Post-mortem examination showed considerable fibroblastic reaction (Fig. 11) and response about the area whereupon cellophane had been placed. This was not confined entirely to the area of aneurysmal disease, but also involved the overlying pericardium and the portion of the left auricle which was in contact. An extremely small area of myocardial infarction in the terminal portion of the area of distribution of the anterior descending coronary artery was also present but was not felt to be of sufficient size to explain the acute fatal episode. Therefore, the presumptive opinion was that there are certain dangers inherent upon allowing irritative cellophane to come in contact with the auricular wall. The supposition is made that hyperirritability may be produced with consequent disturbance of both the pacemaker and conduction mechanisms. Certainly a solitary clinical experience of this type does not justify the formation of any permanent conclusions, but does indicate the need for further animal experimentation in this regard. Also, it is felt that until further data are obtainable, should one place cellophane within the pericardium, the addition of an external, nonirritative layer would appear to be indicated.

Our most dramatic clinical application of this procedure occurred early in the investigative period. A white man of 52 years (Fig. 12), with known positive serology, was admitted to the Grady Memorial Hospital in critical condition secondary to massive hemoptysis. Studies revealed the presence of a large aneurysm, occupying the mid-portion

of the aortic arch and a second, even larger, aneurysm was present in the descending thoracic aorta just above the left diaphragm. The patient described very definite localizing symptoms as to the origin of the pulmonary bleeding, namely, at the base of the left lung. This patient continued to bleed very actively and it appeared that a fatal issue would ensue unless heroic measures were attempted.

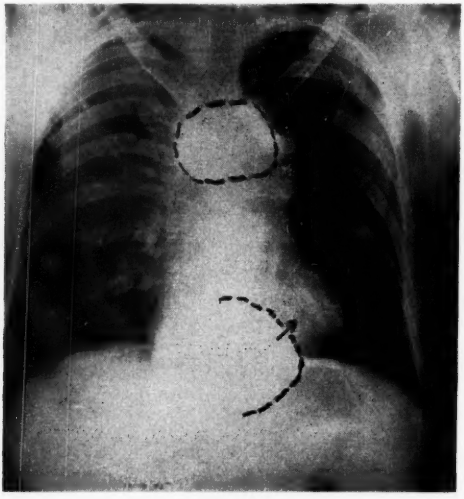
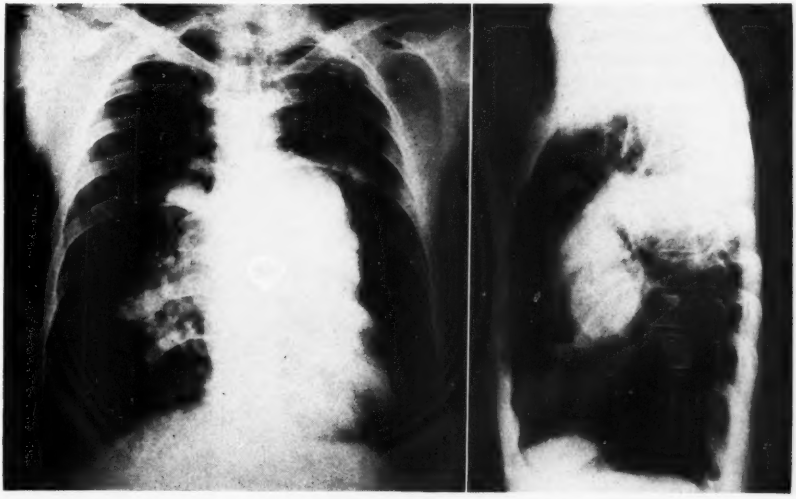


Fig. 12.—Patient, Mr. S. N. Posteroanterior x-ray view of the chest, showing the presence of multiple aortic aneurysms due to syphilis. Superimposed on this area are drawn the outlines of the large aneurysm of the mid-portion of the aortic arch as well as the supradiaphragmatic aneurysm with its point of communication with the right lower lobe of the lung.

Therefore, the patient was taken to the operating room, and through a left transpleural approach the aneurysm of the descending thoracic aorta was visualized, and a definite aortopulmonary fistula was found to be present. The adherent overlying lung was freed up and the fistulous communication clamped off at a 1 cm. distance from the aneurysm and transected. Therefore, a small portion of the lung was left adherent to the aneurysm and utilized in the closure of this area of defect in the aneurysmal wall. A free pleural graft was then placed over this area of repair in the aneurysmal wall and this aneurysm was surrounded with four thicknesses of Polythene cellophane. The defect in the left lower lobe was closed with interrupted silk sutures.

In view of the patient's general condition the second aneurysm which occupied the mid-portion of the aortic arch was not treated at this time. The patient's recovery was uneventful and he returned to a gainful occupation for a period of five and one-half months. He refused further surgery in relation to the aneurysm of the aortic arch. The patient died suddenly five and one-half months following surgery, but post-mortem examination was not permitted. For three weeks prior to death the patient had shown signs of increasing obstruction to the trachea and there was considerable hemoptysis at the time of his sudden death. It is suspected that the upper aneurysm may have eroded the trachea but exact knowledge in this regard is not available. It is felt, however, that this patient demonstrates a definite application for this method of procedure in the presence of fistulous communication between an aortic aneurysm and the pulmonary tree.

In only one other instance in our study group has this procedure been applied as an aid in the control of massive pulmonary hemorrhage. This patient is a 34-year-old white man (Figs. 13, 14, 15) who has been known to have some cardiac anomaly throughout his life. A cardiac murmur is stated to have been noted at the age of 6 years, with no antecedent history to suggest rheumatic fever. No cyanosis had been noted prior to the age



A. *B.*

Fig. 13, *A* and *B*.—Patient, Mr. T. F. L. Posteroanterior and left lateral roentgenograms showing massive aneurysmal dilatation of the pulmonary arteries, more marked on the left. Note particularly the "pseudo-embryo" shadow in the lateral projection. This type of shadow was seen in both patients having congenital aneurysms described in this communication.

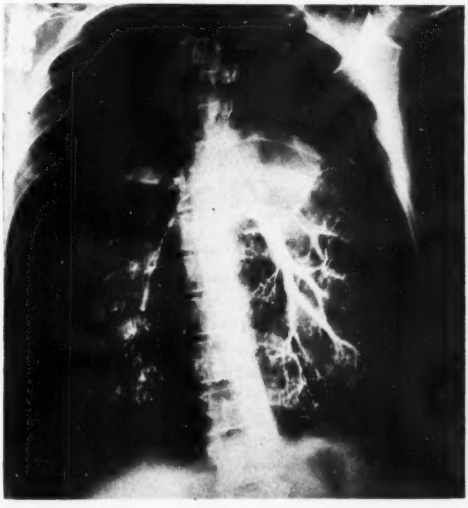


Fig. 14.—Patient, Mr. T. F. L. Lipiodol bronchogram demonstrating massive enlargement of the left pulmonary artery producing compression of bronchi most marked upon posterior segment of the left upper lobe.

of 29 years. At that age the patient began to note frequent recurring episodes of pneumonitis occurring with essentially equal frequency on the two sides of the chest. Increasing wheezing, cough, and occasional hemoptysis had been noted since the age of 31 years. Two years prior to seeing this patient, x-ray studies were carried out and a tentative diagnosis of mediastinal lymphoma made. He received two courses of deep x-ray therapy without change either in symptoms or x-ray findings.

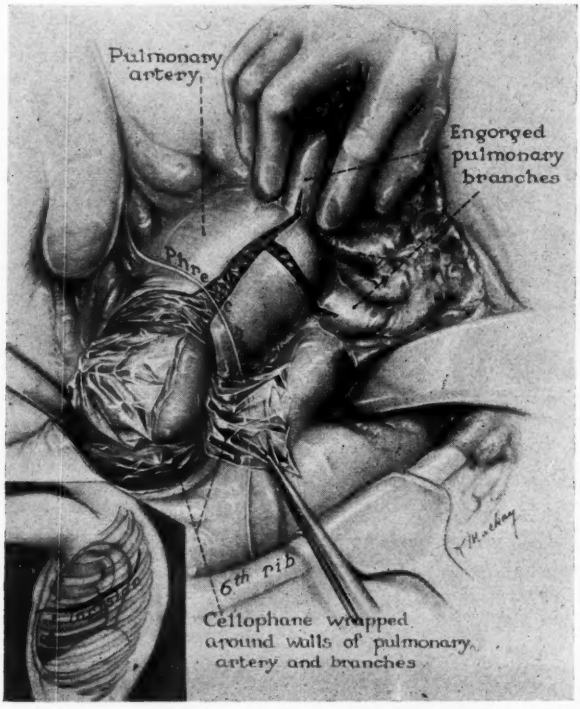

Pulmonary artery
Engorged pulmonary branches
6th rib
Cellophane wrapped around walls of pulmonary artery and branches

Fig. 15.—Patient, Mr. T. F. L. Artist's drawing showing Polythene cellophane being applied to massive aneurysm of left pulmonary artery. This substance was also placed about the segmental branches going to the left upper lobe. Insert at left shows the high lateral approach used.

This patient was first brought to my attention October, 1945, and was noted to have marked clubbing of the fingers, definite cyanosis, and a loud systolic murmur present in the second and third interspaces to the left of the sternum. Lipiodol studies presented evidence of massive enlargement of the pulmonary arteries, particularly the left pulmonary artery, and considerable secondary obstruction to the bronchial tree was noted. Cardiac catheter investigation revealed an extremely high pressure in the right ventricle, namely, 125 mm. of mercury, compared with a systolic blood pressure of 109 in both arms. The marked elevation of the pressure within the right ventricle was corroborated on two subsequent cardiac catheter studies, but these three studies showed some variance in the relative oxygenation of the blood obtained from the superior vena cava, right auricle, and right ventricle. On one of these examinations the examiner felt quite certain that he was able to pass the catheter into the left auricle through a large interatrial septal defect. During the subsequent two cardiac catheter studies this finding could not be corroborated.

The patient underwent angiocardiography on two occasions, but the findings were inconclusive relative to the presence of an atrial septal defect. He was kept under observation, and on Jan. 12, 1946, was admitted to the hospital apparently in extremis and

suffering from extremely copious hemoptysis. The patient localized the site of bleeding in the region of the left upper lobe. The pulmonary bleeding persisted in such an active form that operative intervention was felt indicated. A left transpleural approach was used, revealing an extreme massive dilatation of the left pulmonary artery, such that at the point of emergence of this vessel from the pericardium its transverse diameter was found to be 12 cm. This dilatation appeared uniform throughout the course of the vessel and its primary branches, particularly to the left upper lobe. The vessel was therefore surrounded with two layers of Polythene cellophane and the branches to the apical and anterior segments of the left upper lobe were similarly surrounded, inasmuch as there was objective evidence of considerable saturation of these two segments with extravasated blood. In view of the extremely high pressure known to exist in the right ventricle and pulmonary artery it was felt unsafe to transect these two branches and it was also feared that suture lines might not hold in such a diffusely diseased vessel.

The postoperative course was essentially uneventful and two months following surgery the patient was able to return to gainful occupation. He has been kept under observation since that time and subsequent cardiac catheterization studies have shown an actual increase in the pressure present within the right ventricle. There has been a very definite improvement in the aeration of the left lung, but no dramatic evidence of decrease in size of the aneurysmal dilatation of the left pulmonary artery has been noted upon x-ray studies. It does appear to have considerably less pulsation visible on fluoroscopy than that noted on the right, and the right pulmonary artery appears to have increased somewhat. The patient has progressed sufficiently well clinically that we have not felt justified to carry out what is still an experimental procedure in regard to the right pulmonary artery. There has been no recurrence of hemoptysis, and although the patient shows some evidence of persistent decreased pulmonary and cardiac reserve, as well as an increase in pressure in the right ventricle, it is felt that operative interference has proved of clinical benefit to him.

A second patient (Figs. 16 and 17) with an unusual type of congenital vascular anomaly and associated aneurysm came under observation in March, 1947. This patient was a 27-year-old white man, a veteran, who had been complaining of some discomfort in the upper substernal area and left side of the chest for five months. X-ray examinations elsewhere had been interpreted as showing evidence of mediastinal lymphoma and the patient had been given a course of deep x-ray therapy. On examination at this hospital a very marked discrepancy between the systolic blood pressure in the right and left arms were noted, namely, a pressure of 130 in the right arm and 96 in the left. A machinery type of systolic and diastolic murmur was found to be present in the second left interspace, which could also be well heard in the left interscapular space. Fluoroscopic studies indicated a pulsatile character to the mass, and angiocardiogram was carried out. A diagnosis of unusual multilocular type of aneurysm of the descending portion of the thoracic aorta was made, and the patient was therefore subjected to exploratory left thoracotomy.

A most unusual condition was presented. There was no evidence of persistence of the ductus arteriosus. The descending portion of the aortic arch appeared to be made up of two parallel vascular tubes, with a communication between these two arteries, similar to that which might be formed by a side-to-side type of anastomosis. Thus, as one followed the aortic arch the left carotid artery appeared to arise in a normal position, as also did the left subclavian artery, except for the presence of definite aneurysmal disease involving its base and proximal 3 cm. The aortic arch then continued downward for approximately 2 inches and stopped as a blind end. This structure lay medial to another vascular tube which arose as a blind end 2 cm. distal to the base of the left subclavian artery, continued down lateral to the original tube forming the blind end of the descending arch, and then continued on downward as an apparently normal descending aorta. A very strong to-and-fro thrill was present over the point of side-to-side communication of these vessels, and a cluster of extremely thin-walled, cherry-sized aneurysmal structures presented about the entire area in which these two arteries were in apposition. The most advanced area of aneurysmal disease was noted at the blind end of the proximal limb and

on the upper lateral wall of the distal limb, and these are the areas where it would appear there would be the greatest degree of intra-arterial pressure. In many areas these points of aneurysmal disease were so thin-walled as to be almost transparent, and it was not felt safe to remove the overlying pleura in all areas. There was also considerable disease on the posterior aspect of the anomaly eroding into the dorsal vertebrae.

Partial application of cellophane was therefore carried out, as it was felt impossible to free the area from its points of contact with vertebral erosion. The patient's post-operative course was uneventful and he was discharged from the hospital six weeks following surgery. However, one month thereafter the patient experienced severe lancinating pain in the upper left posterior part of the chest in conjunction with rather boisterous

Fig. 16.

Fig. 17.

Figs. 16 and 17.—Patient, Mr. K. L. Fig. 16 shows the posteroanterior x-ray view of the chest. Note the rather vague nodular shadow in the region of the poorly outlined aortic knob. Fig. 17 demonstrates the filling of this shadow with 70 per cent Diodrast proving the presence of a congenital aneurysm of the aorta.

laughter. This pain persisted and the patient returned to the hospital, showing evidence of marked enlargement of the aneurysmal shadow. There was rather rapid onset of atelectasis in the left upper lobe thereafter, associated with an acute inflammatory reaction. The response to chemotherapy was slow and incomplete and the upper lobe showed evidence of multiple areas of abscess formation.

Cautious bronchoscopic therapy was then instituted with gradual but definite benefit to patient. Two weeks later the patient began to present increasingly severe hemoptysis which subjectively was arising from the left upper lobe area. He showed increasing blood pressure in the right upper extremity, and decreasing systolic blood pressure readings in the left upper extremity and in the legs. The patient finally died four and one-half months following cellophane application to the aneurysm with an episode of exsanguinating hemoptysis.

Autopsy was performed and it was found that the area of aneurysmal erosion, posteriorly, had probably leaked on several occasions and markedly displaced the cellophane from its original point of application. In fact, a considerable amount of hematoma fluid was present between the cellophane and the original aneurysmal wall, and the amount of reactive thickening of the wall was extremely disappointing. Fistulous communication between the areas of false aneurysmal sac at the left upper lobe bronchus was found, and no cellophane was found in this area. It was felt not to have played a role in the formation of this fistula. The lack of reaction about this aneurysm was felt to be due either to the early interposition of hematoma fluid between the aneurysmal wall and the overlying cellophane, or possibly due to the fact that the cellophane utilized had been kept in alcohol for several weeks prior to its application. There were not sufficient data available at this time, but it was believed that to prolong the soaking of Polythene cellophane in alcohol appears to diminish the degree of tissue reaction.

In general, this substance has been subject to rather severe clinical tests inasmuch as the procedure is still considered to be experimental, and therefore one is only justified in utilizing what appeared to be otherwise hopeless cases.

The first patient (Fig. 18) in whom this procedure was carried out at the Grady Memorial Hospital is a 48-year-old colored woman who first presented a baseball-sized aneurysm projecting through the right anterior chest wall and having partially destroyed areas of the first, second, and third ribs on the right, anteriorly. This lesion showed marked pulsation, and x-ray examination revealed the presence of a huge upper mediastinal mass. The patient was operated upon in October, 1945, through a right transpleural approach, revealing the presence of a massive aneurysm involving the ascending aorta and innominate artery, with a considerable area of overlying false aneurysmal sac. The superior vena cava was markedly flattened and widened. The aneurysm could not be totally surrounded but Polythene cellophane was applied to as much of the presenting surface as possible and about the base of the area of extension of the aneurysm through the anterior chest wall. The intrathoracic portion of the aneurysm having been treated, it was planned to carry out application of the irritative substance to the extrathoracic portion of the aneurysm at a subsequent stage. This aneurysm was syphilitic in origin. The second operative procedure was refused by the patient.

The immediate postoperative course was remarkably uneventful and during the ensuing months the area of visible and palpable extrathoracic aneurysm was seen to recede completely and lose its pulsatile quality. The patient did well for twenty-one months following surgery, at which time there began to be a gradual re-enlargement of the following antethoracic area of aneurysmal disease. The patient has continued to refuse further surgery, and this area has been noted to enlarge slowly and gradually up to the present time. It has now almost achieved its original size. The patient is now alive, thirty-one months following original application of cellophane.

The original intrathoracic shadow showed the typical initial period of primary enlargement, and has since returned to essentially its original size. At the time of cellophane application lipiodol was inected subpleurally over the lateral extension of the aneu-

rysm, and this has been followed on subsequent x-ray studies and has been noted to move medially 1 cm. closer to the midline than it was at the time of immediate postoperative films.

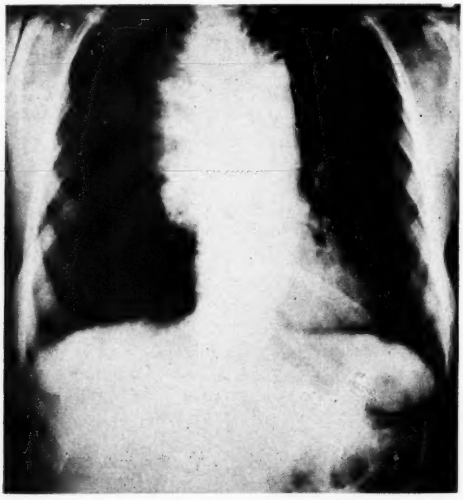


Fig. 18.—Patient, Mrs. M. J. This patient has a massive aneurysm of the innominate artery with a large false sac. The lesion had eroded through the anterior thoracic wall, presenting under the skin prior to cellophane application. Patient was still alive two years later.

One other type of aneurysm has been dealt with in this study, namely, dissecting aneurysm of the thoracic aorta. The application of this method of attack to this type of lesion appears very questionable on theoretical grounds. It has seemed justifiable to apply this method in rather desperate-appearing cases, especially with the plan in mind of application of the irritative substance to the aortic wall, proximal to the area of dissecting aneurysm. Particular attention has been paid to this factor because of the tendency for these lesions to dissect proximally and terminate with fatal rupture into the pericardial sac.

Two patients with dissecting aneurysm of the descending portion of the thoracic arch and the entire descending thoracic aorta have been operated upon. The first patient (Fig. 19) was operated upon in December, 1945, and a massive aneurysm found to be present. Cellophane was applied over the entire course of the aneurysm, with particular attention to surrounding the aorta with cellophane in the area of the transverse portion of the thoracic arch, extending two inches immediately above the apparent site of origin of dissection. This patient survived twenty-five months following the operative procedure. No dramatic change in the size of aneurysmal disease was noted. The patient was a narcotic addict prior to the time of cellophane application and continued to be, thereafter. He did not return to gainful employment. He did experience an episode of acute upper abdominal pain seventeen months following the original intrathoracic procedure, which was found to be due to a perforation of a peptic ulcer of the duodenum, which responded well to immediate surgery. The patient experienced considerable decreased respiratory reserve due to extrinsic compression by the aneurysmal mass upon the left lung. This phenomenon was present prior to operation and was not markedly benefited by the procedure. The patient died suddenly twenty-five months following the original operation and unfortunately post-mortem examination could not be obtained.

A second patient (Fig. 20) with a fairly similar, but less advanced, stage of disease of dissecting aneurysm was treated in April, 1947. This patient was seen two weeks following apparent original episode of dissection of the aortic wall and was treated by bed rest for six weeks. He experienced persistent pain and extremely rapid weight loss. The serology in both patients with dissecting aneurysm showed no evidence of syphilitic disease.

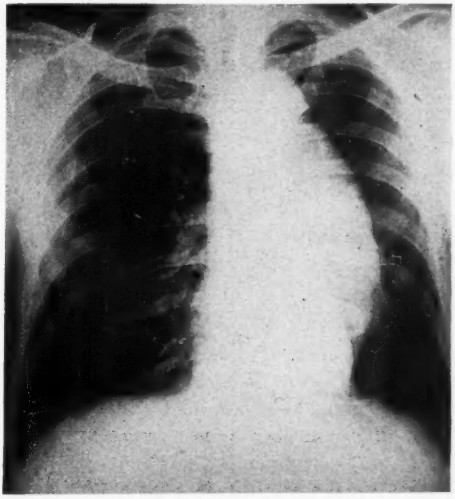
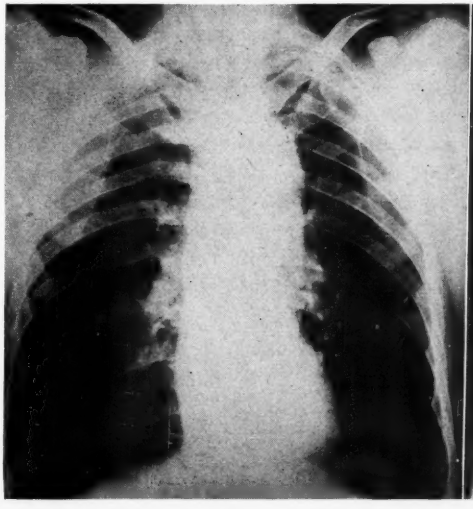


Fig. 19.—Patient, Mr. J. C. C. This x-ray film illustrates a massive dissecting aneurysm of the descending thoracic aorta. Note the associated emphysema and compression-type atelectasis of the left lung.



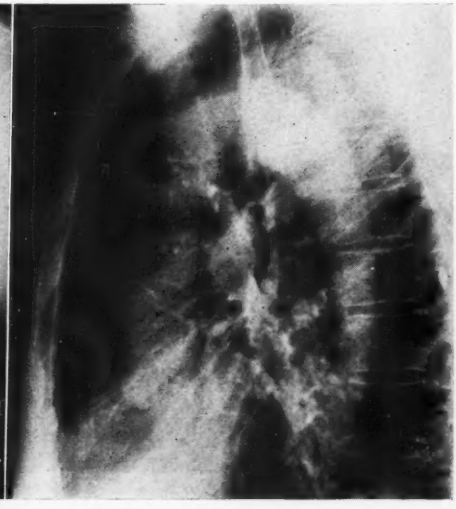


Fig. 20. Fig. 21.

Fig. 20.—Patient, Mr. T. F. T. Posteroanterior x-ray view showing the shadow cast by a dissecting aneurysm of the aortic arch and upper portion descending thoracic aorta.

Fig. 21.—Patient, Mr. T. F. T. Angiocardiogram taken in the left lateral projection. Note the double shadow presented. The dense shadow is produced by Diodrast passing through the normal lumen; the lighter shadow represents the area of dissection.

Eight weeks following the original acute episode, the second patient was studied by angiocardiography and a very good demonstration of the lesion was obtained (Fig. 21). It was possible to carry out complete surrounding application of cellophane to this lesion, involving considerable area of the aorta above and below the points of dissection. The patient experienced no difficulty following surgery, and two months after operation had regained the thirty-five pounds which he had lost and returned to his previous gainful occupation. He has had no symptoms since that time and the x-ray studies show no visible change in the size of the original lesion. There has been no change in the blood pressures in the upper and lower extremities, postoperatively, in comparison to those obtained prior to surgical intervention. The progress of this second patient has been very gratifying to date, but it is felt that until further data become available that it is perfectly possible that a similar pleasing course might have occurred had no surgery been performed.

At the completion of the first year of this study, our data were reviewed and we were impressed by the fairly uniformly satisfactory results which had been obtained in patients in whom the entire area of aneurysmal disease could be surrounded by cellophane. However, the majority of patients presented lesions in which a large area of the aneurysm could not be surrounded, due to erosion into overlying or underlying bony structures. In 40 per cent of these patients we did apparently achieve a definite decrease in the amount of pain experienced by the patient by the application of this substance. In the other 60 per cent no apparent benefits were obtained. In the majority of these patients follow-up studies have demonstrated a progression of their disease and fatal issue has occurred in 65 per cent from two to fourteen months following surgery.

Realizing the variance in prognosis and duration of life with this type of aneurysm, it is not felt that life has been prolonged in any of these patients, and the only benefit noted in these advanced cases has been reduction of pain in 40 per cent. Furthermore, the majority of these patients have died within four months of institution of operative therapy and it has been felt that this type of lesion needs a combination of methods in the therapeutic approach. Therefore, in four instances during the past year patients with advanced aneurysmal disease have been treated by a combination of partial cellophane application, plus internal wiring. In one patient with a very massive aneurysm of the transverse and descending portions of the aortic arch, this procedure was carried out and the patient died suddenly ten days following surgery and was found, at autopsy examination, to have delivered a large embolus up through the left common carotid artery. A considerable amount of fresh clot was noted within the aneurysm, and there appeared to be adequate early, peri-arterial reaction.

Two other patients with lesions of the descending thoracic aorta have been similarly treated, and now at three and five months postoperatively they appear to be progressing satisfactorily. A fourth patient (Figs. 22, 23, 24, and 25) with similar disease was operated upon ten months before this communication, and his course has been sufficiently dramatic that it is felt worthy of specific note. This patient was a 48-year-old colored man, a veteran, who was sent to the Lawson Veterans Administration Hospital. The lesion had progressed to sufficient size that the overlying skin showed definite early ulceration. Immediate surgical intervention was felt indicated, so that a right anterior transpleural approach was utilized. It had been hoped that it might be possible to occlude the innominate at its base, but the area of aneurysmal disease was found to extend for a considerable distance down the ascending aorta so that cellophane was applied about the base of the innominate artery, as well as the area of disease of the ascending aorta. This substance was also applied, to as great an extent as possible, about the innominate artery.

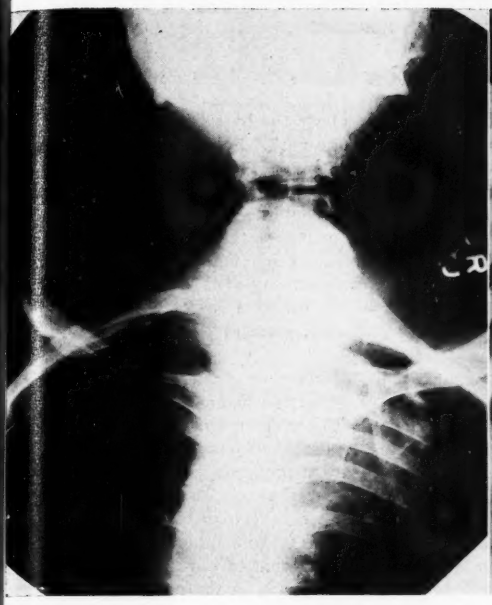


Fig. 22.

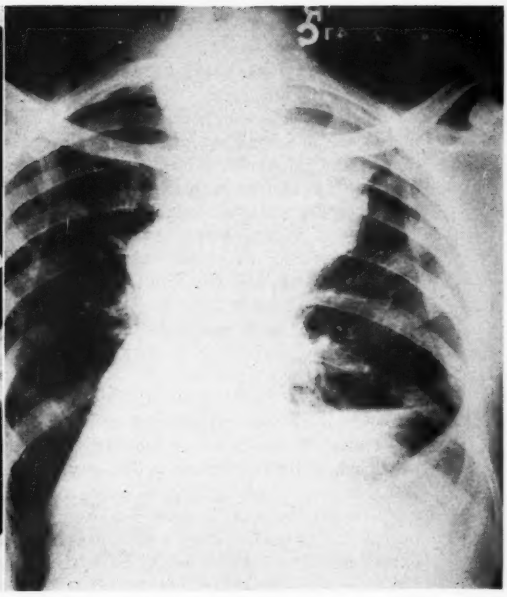


Fig. 23.

Figs. 22 and 23.—Patient, Mr. A. M. Fig. 22 illustrates the large aneurysm of the innominate artery plus the large false-sac in the suprasternal area. Fig. 23 represents an x-ray view taken six days following surgery. The false-sac has refilled following the original aspiration. Silver wire placed in this sac does not show up well on the film.

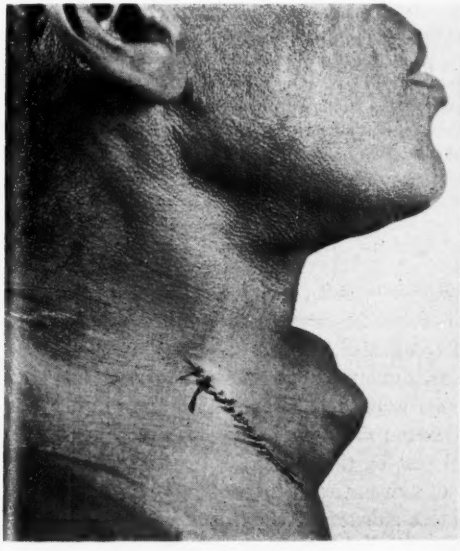


Fig. 24.

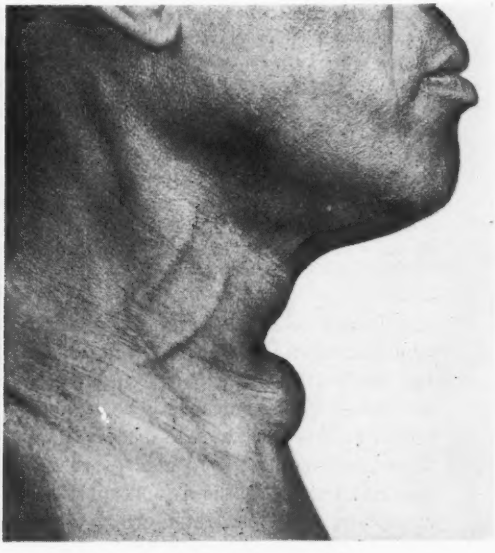


Fig. 25.

Fig. 24.—Patient, Mr. A. M. Photograph to show profile of cervical false-sac three months after original cellophane wrapping and wiring operation. Cervical incision had been made for proposed purpose of inserting additional wire but aspiration revealed original communication with parent aneurysm was now occluded. Irregular contour in this photograph is produced by the contained wire after contents were aspirated.

Fig. 25.—Patient, Mr. A. M. Profile photograph taken ten months after original operation. Lesion has since become progressively smaller and now measures 1 cm. in diameter. Patient is clinically well.

It was felt that we were able to apply the substance to approximately 80 per cent of the surface of the aneurysm.

Particular attempts were made to place the cellophane about the base of the projection of the aneurysm up into the false sac which presented in the neck. Following application of the substance, a large spinal needle was introduced through the wall of the aneurysm up into the sac presenting in the neck. There appeared to be evidence, upon insertion of the needle, that the inner wall of the innominate aneurysm contained a thick layer of blood clot. It was found that the projection of the aneurysm up in the neck could be aspirated of old hematoma fluid, and that the area of communication with the primary aneurysm was apparently small as evidenced by relatively slow refilling of the aneurysmal sac. A considerable amount of silver wire was then injected into this sac through the spinal needle before mentioned, and the chest wall closed after removal of the needle and application of fibrin-foam to the site of needle puncture.

The patient's postoperative course was complicated by a certain amount of atelectasis and episodes of paroxysmal auricular fibrillation. An outer protective layer of nonirritating cellophane was not utilized as much as it was felt that the area of ascending aortic aneurysmal disease did not necessitate the application of irritating cellophane in a region which might irritate either auricular or ventricular wall. The patient's progress was slow and the area of aneurysm presenting in the neck remained approximately 60 per cent of its preoperative size, became definitely less pulsatile, and allowed the overlying skin to resume the normal texture and appearance. Two months following the original operation it was considered that it might be advisable to implant a larger amount of silver wire into the false sac presenting in the neck. Therefore an incision was made in the neck, on its right lateral aspect, and the wall of the aneurysmal sac visualized. The needle was inserted into this wall. A surprisingly thin type of hematoma fluid was encountered which was aspirated. The original wire could be palpated at this time.

Surprisingly, there appeared to be no tendency for this sac to refill, so that the operative procedure was terminated and the patient returned to the ward. The false aneurysmal sac in the neck was noted to re-enlarge gradually over a period of eight days. A needle was again re-inserted into the sac through the tissues of the neck and the cavity evacuated. Further observation revealed that this procedure was necessary at about seven- to ten-day intervals and he was returned to another veterans' facility three months following the original operative procedure. Ten months after the original operation the patient presented a small firm nonpulsatile lesion in the supersternal notch measuring 2 cm. in diameter and he has not required aspiration for the past five weeks. No appreciable change in the size of the intrathoracic masses is noted on subsequent x-ray studies. It is now planned to study the lesion with angiocardiographic visualization and to follow the patient periodically. It is felt that this patient has demonstrated unequivocal evidence of the value of a combination of methods of approach to an advanced aneurysmal lesion.

SUMMARY AND CONCLUSIONS

I wish to re-emphasize that this report must be considered preliminary in type and that the findings to date are not conclusive. This study has involved the application of experimental methods to human aneurysmal disease in 23 patients. The experimental character of this approach has required the application of this substance to disease in an advanced and apparently hopeless stage. This has produced a rather severe clinical test of the method. Unfortunately this has required that a large percentage of the patients present lesions which cannot be totally surrounded by the irritative substance, Polythene cellophane. The results have been strikingly and uniformly more beneficial in those patients in whom total surrounding of the lesion has been achieved.

The majority of the lesions treated have been of syphilitic origin. Unfortunately, in the main, these patients have been members of the indigent, colored, and lower intelligence bracket. This factor has markedly hindered the adequacy

of follow-up studies and, in particular, has permitted remarkably few post-mortem examinations in patients wherein a fatal conclusion occurred. In certain instances, falsification of name and address have deprived us of any follow-up knowledge of patients following their discharge from the hospital. Adequate clinical follow-up studies and tissue examination, to demonstrate the effect of Polythene cellophane upon the human tissues, is not available. Certain errors in the management and technique of the treatment of these patients have occurred, especially in the early stages of this study, and we have felt that it is particularly important for this communication to draw special attention to these failures. Certain methods which we have instituted in order to eradicate the repetition of such disasters have been described.

We wish particularly to re-emphasize the danger of separating an area of aneurysmal disease from a point of bony contact. Furthermore, we have attempted to stress the frequency with which aneurysmal disease in proximity to the trachea or main stem bronchus may produce an extremely diminished vital capacity, pronounced endobronchial or endotracheal edema, and preclude the possibility of open thoracic procedures until certain corrective measures have been instituted. We have utilized two main methods of enlargement of the thoracic inlet. In patients in whom the primary disease is at a sufficient distance from the upper sternum, a one-stage split of the sternum with application of internal supportive splints to maintain the spreading of the sternum is recommended.

In the majority of the patients we have found it necessary to utilize a second type of decompression, namely, removal of a portion of the clavicle and first two ribs with particular attention to transection of the ligaments behind the clavicle to allow anterior elevation of the sternum. It has usually been found necessary to carry out this procedure bilaterally, and it should not be done under general anesthesia. The patient may note immediate clinical benefit relative to respiratory capacity following this decompression measure, but it is our experience to note that it usually requires from two to four weeks for adequate re-aeration of the lung to occur and edema of the airway to disappear.

One is impressed with the value of angiocardiographic visualization in patients having unexplained mediastinal masses or known aneurysmal disease when surgery is considered. It seems that approximately 70 per cent of aneurysms of the major thoracic vessels do not show evidence of pulsation on fluoroscopy, and this is felt to be due to either marked thickening of the perivascular structures, intra-aneurysmal formation of clot, or a combination of the two. It is felt important to stress the frequency with which aneurysmal disease may be multiple when one is confronted with a patient having aneurysms secondary to syphilis.

The technique of the sterilization and application of Polythene cellophane has been described. Particular stress has been placed upon the need of fixing this material to the aneurysm, or to surrounding structures, to prevent its displacement following operation. Further investigation is required relative to the optimum of time for soaking this material in alcohol, but the early impression is gathered that immersion in alcohol longer than forty-eight hours may decrease the efficiency of the irritative mechanisms.

The later stages of this study have shown it advisable to use a combination of therapeutic approaches to aneurysmal disease wherein complete surrounding of the lesion is not possible. We have utilized a combination of application of cellophane externally, and internal wiring. In three of four instances this has been felt to provide a definite improvement on the previous method of a solitary therapeutic approach to these advanced lesions.

To date I have applied cellophane to thoracic aneurysms in thirty-two instances, using the addition of internal wiring in four of these patients. The majority of the lesions have been syphilitic in origin. Two patients having aneurysmal disease presumed to be congenital in origin have been treated. In one of these the lesion was a diffuse aneurysmal dilatation of the pulmonary artery, probably secondary to a massive interatrial septal defect. In the second patient a most unusual congenital anomaly of the descending portion of the thoracic aorta was presented. This lesion could not be completely surrounded and definite benefits from this type of surgical intervention were not obtained. Should such a lesion be again encountered one would have to consider strongly the resection of this area of the aorta and some method of reconstitution of the vascular channel. One aneurysm of the main pulmonary artery was treated, which was found to be in association with diffuse sclerosis of the pulmonary and systemic arteries in a young female. It is doubtful whether this procedure would have benefited the patient had a successful postoperative course occurred. It is felt that this patient presents evidence that irritative cellophane should not be allowed to come in contact with irritable areas of the heart wall. It is felt that when the substance is placed within the pericardium an inner layer of nonirritative cellophane should be utilized.

This procedure has been applied on two occasions in our series in the presence of active, massive hemoptysis. In one of these instances it was used as an aid in the closure of a fistula between the aneurysm and the lung.

In conclusion, it is felt from these studies that a sufficient amount of benefit has been derived in these far-advanced patients to consider continued use of this method of therapeutic approach. The combination of the indirect methods of correction of aneurysmal disease probably presents certain advantages, not inherent in any one method of indirect approach alone.

ADDENDUM

Further experience has shown the Polythene cellophane should be prepared by steam sterilization for twenty minutes. Alcohol may discolor the initiating substance dicetyl phosphate.

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DISCUSSION

DR. J. KARL POPPE, Portland, Ore.—I want to congratulate Dr. Abbott on his relatively large series of cases for this early stage in the surgical control of intrathoracic aneurysms.

During the past two years I have run across approximately a dozen aneurysms, of which only six were actually operable. The majority of these inoperable cases were in cardiac decompensation as a result of dilatation of the aortic ring and aortic insufficiency. A certain number of the patients were too advanced in age to consider for any major surgery. I think that applied to all of the arteriosclerotic dissecting aneurysms I saw. The patients were all over 70 years of age, with an absence of pulsation in the lower extremities.

The procedure seems a little too early in its infancy to permit undue risks in accepting this type of patient. Other contraindications were complete compression and stenosis of the main bronchi, which seemed to contraindicate any major surgical procedure.

I am very happy to have been able to contact the first patient in whom we used Polythene cellophane. The social service here in St. Louis located this patient yesterday—twenty-three months postoperatively.

(Slide.) This type of fusiform aneurysm of the descending aorta still seems to be the most satisfactory one of the group for cellophane wrapping. This was the first patient whose aneurysm was wrapped with Polythene cellophane. He is now twenty-three months postoperative and working every day. He was on relief for at least two years, suffering very severe pain in the back and a throbbing pain in the anterior part of the chest, which I understand has been relieved.

(Slide.) There is another type of aneurysm which has proved very satisfactory—a fusiform aneurysm of the descending aorta, plus the distal part of the arch.

The picture on the right was taken two months postoperatively, and that seems fairly characteristic of these postoperative films in that there has been no apparent decrease in the size of the shadow, that the compression apparently occurs internally, and the shadow on x-ray examination may even increase in size.

(Slide.) This represents another fairly satisfactory aneurysm in which we have been unable to evaluate completely the results, due to the presence of generalized arthritis in this patient. Some days he feels he is cured and then again, on rainy days, he complains of generalized aches all over the body.

(Slide.) I am showing this slide partly for Dr. Renault de Oliveira who has returned to Brazil. This was one of the original dog aortas wrapped with Polythene cellophane. A normal section of the same dog aorta is on the right side.

(Slide.) Dr. de Oliveira carried out further experimental work in an attempt to cover the active polythene cellophane with a nonreactive type of material to slip underneath the superior vena cava, for instance, on aneurysms of the ascending aorta.

The picture on the left shows the Polythene cellophane which has been covered with 300 PUT nonreactive cellophane, which apparently reduces the reaction of the Polythene cellophane to such an extent that it seems undesirable to use, except over very limited areas around vital structures. It reduces the external compression so that it detracts from the original purpose of the Polythene.

DR. ABBOTT.—I have very little to add except for the fact that we have had patients in whom there was such a degree of bronchial compression that the physical findings appeared to be those of pulmonary edema and they had been diagnosed as "patients with cardiac failure." Following decompression, these changes were noted to disappear and the patient became eligible for intrathoracic surgery.

I believe that the observation justifies further stress relative to the early increase in the size of the x-ray shadow following operation. We feel that this is due to two factors, namely, (1) the release of the constricting overlying pleura, and, (2) the initial formation of fluid about the cellophane as the fibroblastic reaction is set up.

The observations in this work have lent emphasis to the original findings of Poppe, that considerable, and even dramatic, relief from pain may be obtained when an aneurysm is only partially wrapped. There is no question but that one must not dissect aneurysms away from points at which they press upon bone, for in such areas the wall may be so thin as to cause spontaneous rupture.

ADENOMA OF THE BRONCHUS: ENDOSCOPIC TREATMENT IN SELECTED CASES

MAX L. SOM, M.D.
NEW YORK, N. Y.

IN 1935 Rudolph Kramer and the author[1] reviewed a group of cases of adenoma of the bronchus and referred to the comprehensive publication on these tumors by Wessler and Rabin.[2] We stressed the criteria for the pathologic diagnosis of bronchial adenoma and its differentiation from carcinoma as demonstrated by Rabin and Moolten.[3] A distinction was drawn between the endobronchial, pedunculated, polypoid tumors and the intramural or extrabronchial type of growth. For the latter, lobectomy was recommended.

Twenty-three cases of adenoma of the bronchus were reported, including four instances that were discovered at autopsy. In nineteen cases the diagnosis had been made by examination of a bronchoscopic biopsy. Two of these patients died of hemorrhage and infection and three were not suitable for endoscopic therapy because of extrabronchial extension. The results of the remaining fourteen, adequately bronchoscopically treated patients were submitted. Nine were then considered either cured or symptom-free and five had persistent, minimal symptoms in spite of bronchoscopic therapy, including diathermy and radium.

Results of further observation of these endoscopically treated patients for the following thirteen years reveal the fact that seven remain cured or completely symptom-free. Of the remaining seven, two died of bronchial bleeding and five were advised to have lobectomy. Surgery was recommended in the latter because of exacerbation of lung suppuration with hemorrhage or the impossibility of eradication of the neoplasm by bronchoscopic means. Thus, seven of the original nineteen bronchoscopically treated cases remain cured or symptom-free (Table I).

In the recent literature there has been much critical discussion as to the ultimate value of endoscopic therapy and a definite trend toward surgical extirpation of these neoplasms has resulted. C. L. Jackson, F. W. Konzelman, and C. M. Norris[4] contend that if success is attained in accomplishing drainage and reaeration of the lung, distal to the obstruction, there is no urgent need for surgery. They report twenty cases of adenoma, in seventeen of which symptomatic improvement was obtained by bronchoscopic therapy, only three patients requiring lobectomy. They believe that bronchial adenomas do not metastasize and show no inherent tendency to become malignant. In their opinion, the incidence of extrabronchial growths is overemphasized. Of six cases of adenoma cited by R. Adams,[5] bronchoscopic removal sufficed in two patients and the other four required pneumonectomy.

From the Otolaryngological Service of Dr. Rudolph Kramer, Mount Sinai Hospital, New York.

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TABLE I

Analysis of Results in First Publication, 1935	
23	cases of adenoma originally reported
−4	post-mortem findings—never bronchoscope
19	diagnosed by bronchoscopy
−2	died of hemorrhage and infection
−3	not suitable or refused endobronchial therapy
14	adequately treated cases—by endoscopy
9	cured or symptom-free
5	persistent minimal symptoms
Results After 13 Years' Additional Observation, 1948, on the Above 14 Cases	
7	cured or symptom-free
2	died of bronchial bleeding
5	referred for surgery

John R. McDonald[6] reported thirty-eight cases of adenoma, twenty-three of which adenomas were diagnosed bronchoscopically. In the remaining fifteen, the microscopic diagnosis was established from surgically removed lungs and post-mortem material. In this group of fifteen gross specimens, they found tumor invasion of the bronchial wall in thirteen. Only two showed no infiltration of the neoplasm intramurally or peripheral to the bronchial cartilage. In the latter two specimens the main mass of tumor was within the lumen of the bronchus.

One must not be too impressed by the high incidences of bronchial wall infiltration in this group of fifteen patients because, ostensibly, they represent conditions not suitable for endoscopic therapy and hence treated surgically. McDonald[6] refers to an isolated endobronchial tumor which was 1.8 cm. in diameter, with a pedicle of but 3 mm. on cross section. In one case infiltration of the lymph node due to direct invasion was found.

W. S. Tinney[7] discussed the conservative and radical approach in the entire group of cases reported from the Mayo Clinic and recommended surgery if the growth is inaccessible or recurs after removal. Of seventeen cases reviewed by R. Adams[8] of Boston, five patients were treated endoscopically, eleven had resection, and one tumor was an incidental finding.

The more radical approach to treatment of these tumors is suggested by E. A. Graham and N. A. Womack,[9] who believe many adenomas are not recognized until they become carcinomas. They advise surgical removal since they have found repeated evidences of local invasion, involvement of regional nodes, and distant metastases. Support for this view is given by W. E. Adams, P. E. Steiner, and R. G. Block,[10] who reviewed five surgically treated cases of adenoma and found regional lymph node invasion in two instances and metastases to the liver and vertebral column in the others. S. W. Holley[11] presented thirty-eight cases of bronchial adenomas including several cylindromas. He advised lobectomy or pneumonectomy as the preferred treatment because many of the tumors are too large or have infiltrated so that they cannot be entirely removed through the bronchoscope.

Because of the wide divergence of prevailing opinion as to the best approach to the treatment of these neoplasms, a tabulation of the result in our cases was

undertaken. In this communication, fifty endoscopically diagnosed and histologically proved cases of adenomata of the bronchus are reviewed. This group includes the nineteen cases originally submitted and thirty-one additional patients observed since 1935. An analysis of fifteen of these patients who have remained cured or symptom-free after endoscopic treatment is presented. The entire group of fifty will shortly be published by the Chest Service of the Mount Sinai Hospital.

A short description of the histology of adenoma is given, since some of the present confusion in the literature results from the inclusion of cylindromas along with adenomata. Cylindroma, as demonstrated by Kramer and Som,[12] is a variety of mixed tumor which is much more invasive and should not be included within this group. In adenoma the central portion of a bronchoscopic biopsy specimen is usually most representative of the true histology of the tumor. The cells appear in solid alveolar arrangement with a delicate stroma. The individual cells are small and regular. They possess round or oval nuclei containing a fine granular chromatin but no distinct nucleolus. Their shape is generally cuboidal but cylindrical cells are not uncommon. Mitoses are absent. The striking feature of the cells is their uniformity in size, shape, and staining character (Fig. 1).

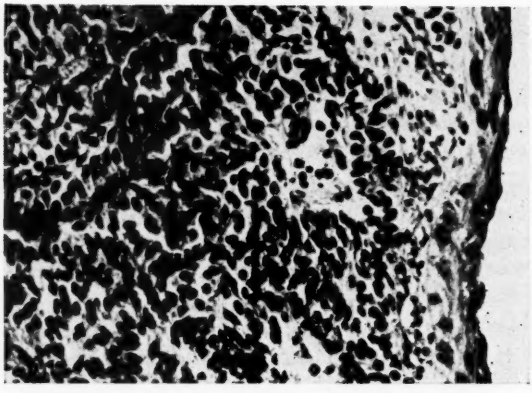


Fig. 1.—Low-power photomicrograph of adenoma showing degenerative changes superficially and solid alveolar structure more deeply.

Viewed either through the bronchoscope or at autopsy, the tumor presents a smooth, polypoid surface, over which the bronchial mucosa is reflected. Prominent vessels may be seen superficially and probably represent the source of bleeding. The endobronchial type of neoplasm has a globular shape which accommodates itself to the lumen of the bronchus which harbors the growth (Fig. 2). These tumors have a limited attachment to the bronchial wall, usually by a pedicle, but occasionally are more sessile. They rarely attain large dimensions since they are confined to the limits of the bronchial wall. In some patients whose conditions permitted bronchoscopic removed of the growth in toto, the size could be accurately ascertained. The tumors usually grow large enough to

occlude a bronchus before producing sufficient symptoms to warrant bronchoscopic examination. The base of the tumor is apparently attached in the submucosa without penetrating the muscular wall of the bronchus. The origin of the neoplasm most probably is associated with either the bronchial glands or their ducts.

The intramural or extrabronchial type of adenoma presents a smooth, broad surface endobronchially, but extends beyond the boundaries of the bronchial wall and projects into the peribronchial tissue. It replaces the bronchial structures and invades the adjacent glands (Fig. 3). In such instances, it may grow to such large proportions as to occupy a large area of the lung parenchyma and cast a dense shadow in the roentgen film.

Fig. 2.

Fig. 3.

Fig. 2.—Intrabronchial adenoma obstructing right main bronchus. The smooth pedunculated tumor is occluding bronchus. Probe inserted into distal bronchiectatic cavity.

Fig. 3.—Intramural adenoma of the bronchus. Localized tumor extending into the peribronchial tissues between the cartilages.

Adenoma of the bronchus is more prevalent among women than men. It may occur at any age but is predominatly a disease of the third and fourth decade of life (Table II). The clinical syndrome and characteristic roentgen findings have been previously presented. An interesting observation in two of our fifteen successfully treated patients was the presence of a normal chest film on inspiration. However, on expiration the mediastinum and the trachea were shifted to the right and there was obstructive emphysema on the left. This was due to the ball-valve action of a pedunculated tumor in the left main bronchus. After bronchoscopic removal, the mediastinal structures returned to normal position (Fig. 4). It should be mentioned that occasionally a pedunculated tumor, although small, may be visualized within the lumen of the bronchus on roentgenographic film.

TABLE II. ANALYSIS OF CURED OF SYMPTOM-FREE PATIENTS

AGE. (YR.)	DURATION OF ILLNESS BEFORE BRONCHOSCOPIC DIAGNOSIS*
29	6 mo.
30	5 yr.
65	7 yr.
42	1½ yr.
32	3½ yr.
31	2 yr.
13	10 mo.
57	3 yr.
35	4 mo.
21	2 yr.
32	1½ yr.
42	6 yr.
32	8 yr.
33	2½ yr.
27	2 yr.
Average 34.6	3.3 yr.

*In 22 male and 28 female patients.

Bronchoscopic examination most often reveals an occlusion of a large bronchus by a pedunculated, easily bleeding, pinkish or purplish growth covered with mucous membrane (Fig. 5). Thirty-four of the fifty patients presented this picture.

This appearance was noted in each of our fifteen successfully treated patients. In the thirty-five endoscopic failures, sixteen showed a stenosis of the bronchus with involvement of bronchial wall on initial examination.

Endoscopic therapy was instituted for all tumors that were interpreted as being of the endobronchial type. Treatment consisted in attempt at removal of the tumor through the bronchoscope and re-establishment of the patency of the lumen. The growths were grasped with bronchoscopic forceps down to and including the attachment. It was not often feasible to accomplish total removal at once, and repeated bronchoscopies were necessary.

In effecting the total removal of the tumor and with a view to prevention of recurrence, diathermy applied to the base has been a valuable adjuvant. Coagulation of the tumor base, especially in instances of local recurrence, has proved a very effective method of eradication of tumor. The most reliable proof that the neoplasm has been completely eradicated is the absence of tumor cells in biopsy specimens from the bronchial wall at the point of attachment of the neoplasm. In our early cases, bronchoscopic implantation of radium into the stump of the adenoma and external radiotherapy were employed.

All patients believed suitable for endoscopic therapy were treated in the above manner until such time as either the growth was eradicated or evidences of extrabronchial involvement were manifest. The endoscopic failures were referred for surgery.

The difficulties encountered in endoscopic removal are ordinarily not great. Troublesome bleeding, especially at early bronchoscopic treatments, may be sufficient to warrant postponement of further removal for several days.

In one instance of an intramural growth, death followed a profuse hemorrhage during bronchoscopic coagulation.

RESULTS

Fifteen, or 30 per cent, of the series of fifty patients with adenoma of the bronchus responded well to endoscopic therapy. Seven of these patients are

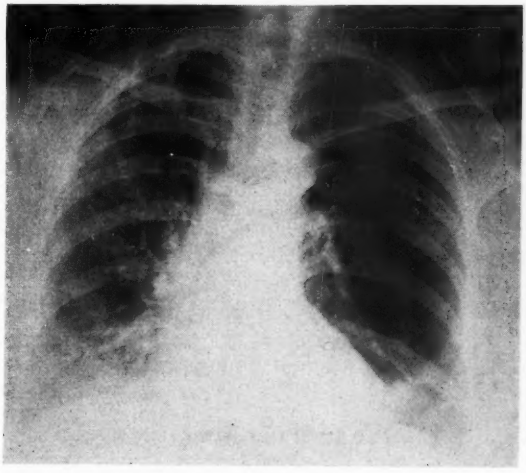


Fig. 4.—Roentgen film on expiration showing obstructive emphysema on the left with shift of trachea and mediastinum to right. On inspiration the film was normal.

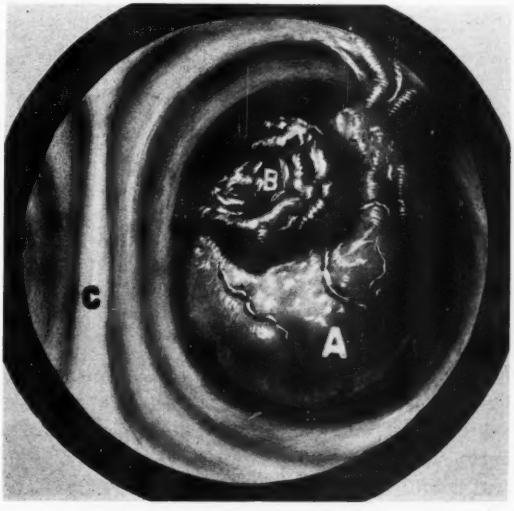
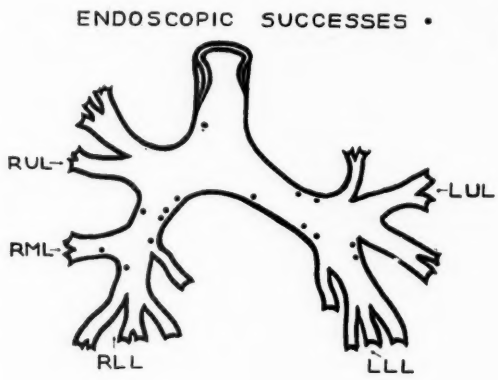


Fig. 5.—Bronchoscopic appearance of adenoma. *A*, Pedunculated adenoma of right main bronchus; *B*, infected thrombus on surface of tumor; *C*, bifurcation of the trachea.

considered completely cured and eight are symptom free. Cures are designated as patients who (1) have an absence of any symptoms referable to the bronchi and lungs, (2) have no abnormal chest findings clinically, (3) have a normal x-ray film of the chest, (4) have a widely patent bronchial lumen on bronchoscopy, and (5) show repeatedly negative bronchoscopic biopsies from the site of the tumor.

Fig. 6.



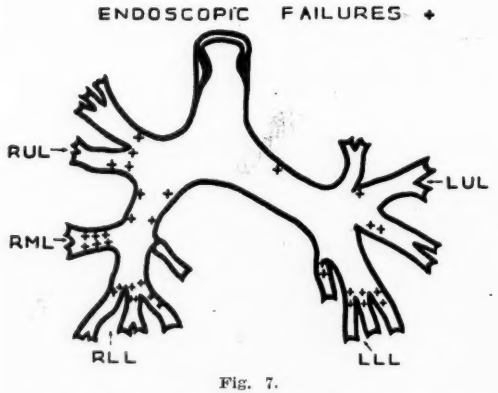


Fig. 7.

Fig. 6.—Location of origin of tumor in fifteen successful cases. Except for the one in the right middle lobe, all were in the main branch or trachea.

Fig. 7.—Location of origin of tumor in thirty-five failures. The branch bronchi are the most frequent sites of origin.

The symptom-free patients have no clinical manifestation of disease. The reason they are not considered completely cured is that they have roentgen evidence of bronchial dilatation. This residual segmental bronchiectasis is not detectable on routine chest film, but can be demonstrated by bronchography. It is of no clinical significance except that there may be a slight cough after an acute upper respiratory infection. In all other respects, these patients are as free of their disease as are those classified as cured.

An analysis of the fifteen successfully treated patients could conceivably aid in the selection of those patients who might be suitable for endoscopic therapy without benefit of surgery. Certain factors would seem to influence favorably the response to conservative treatment; namely, (1) location of the origin of the tumor, (2) duration of illness before institution of endoscopic treatment, and (3) bronchoscopic appearance. These factors will be considered separately.

(1) Location of the Origin of the Tumor.—The location of the tumor in our fifteen successfully treated patients was exclusively in the main bronchus and trachea except for the one which originated in the right middle lobe (Fig. 6). Among our thirty-five failures only five patients had tumors situated in the main bronchi, the remainder being, in order of frequency, in the lower lobes, in the upper lobes, and in the middle lobe bronchi (Fig. 7). This would indicate that the accessability of the tumor to bronchoscopic manipulation could be an important factor in determining success or failure. The anatomic surroundings of the neoplasm and the available free lumen for growth could also be a consideration favoring endobronchial confinement in the larger main bronchi. Many of the neoplasms originating in the branch bronchi often showed early evidence of intramural and extrabronchial spread (Table III). A logical inference could be that the branch bronchus neoplasms are not only less accessible for endoscopic treatment, but also show earlier evidence of intramural involvement.

TABLE III. LOCATION OF ORIGIN OF TUMORS

LOCATION	NUMBER
In Endoscopic Failures:	
Right Main Bronchus	4
Right upper lobe	4
Right middle lobe	6
Right lower lobe	9
Left main bronchus	1
Left upper lobe	3
Left lower lobe	8
In Endoscopic Successes:	
Trachea	1
Right main bronchus	6
Left main bronchus	7
Right middle lobe	1

(2) Duration of Illness Before Bronchoscopic Diagnosis.—The duration of illness before attempt at endoscopic removal in our successful series of fifteen patients was 3.3 years (Table II). If we now compare this with the duration of illness in the five main bronchus adenomas not responsive to endoscopic

TABLE IV. DURATION OF ILLNESS IN MAIN BRONCHUS ADENOMAS NOT RESPONSIVE TO ENDOSCOPIC THERAPY

LOCATION	NUMBER OF YEARS
Left main bronchus	37
Right main bronchus	25
Right main bronchus	30
Right main bronchus	7
Right main bronchus	7
Average	21.2

therapy, we find a vast difference (Table IV). The average duration in these five patients was 21.2 years. This prolonged period not only allows enough time for extrabronchial extension, but also favors the formation or irreparable suppurative disease of the lung distal to the tumor. Both of these conditions require surgery for cure.

(3) Bronchoscopic Appearance.—In all of our successful cases, a smooth globular tumor with a limited attachment was seen bronchoscopically. Stenosis of the bronchus or evidences of extrabronchial compression were seen in sixteen instances, all of which proved not amenable to endoscopic therapy. On the other hand, the finding of a globular smooth mass does not necessarily mean the tumor will permit bronchoscopic removal. The appearance of the bronchus after repeated endoscopic treatment may, however, give a clue to the possibility of cure and the advisability of continued bronchoscopy. In all of our successfully treated patients, the average number of bronchoscopies before the normal architecture of the bronchus could be visualized was three (Table V). In every instance, the normal bronchial markings, including septa and lumina of the branch bronchi, were apparent at the fifth bronchoscopy. Considering that treatment can be given at five-day intervals, it does not appear too protracted a trial period before abandoning attempts at conservative cure. The number of treatments required before the tumor was completely removed and the biopsy reported consistently negative was found to be between three and eight (Table V). The inability to eradicate the tumor completely and visualize the normal architecture of the bronchus after a fair trial period is an indication for surgical intervention.

TABLE V

NUMBER OF BRONCHOSCOPIES BEFORE NORMAL ARCHITECTURE OF BRONCHUS WAS VISUALIZED	NUMBER OF TREATMENTS BEFORE BRONCHOSCOPIC BIOPSY SHOWED NO TUMOR
5	7
2	4
4	5
3	4
2	4
2	5
2	4
3	8
2	4
2	4
3	8
2	4
3	4
3	3
5	6

While no hard and fast rules can be made as to a time limit for cessation of endoscopic treatment, certain findings militate against further treatment. The persistance of a dense shadow in the lung after the endobronchial portion of the tumor has been eradicated is significant. Such densities may well represent either outlines of the tumor mass itself, or adjacent lymph nodes locally invaded by the tumor.

Recurrent hemoptyses and continued exacerbations of the lung suppuration point to the need for surgery. It is important to appreciate that the bronchiectasis distal to the tumor may occasionally be reversible if the obstruction is promptly relieved. Such bronchictasia seems to run a much more benign course than that of ordinary bronchiectasis following suppurative bronchopneumonia. The need for surgical treatment of lung suppuration itself after eradication of the tumor endobronchially is not frequent.

Local endobronchial recurrence of the tumor without evidence of peribronchial spread is not necessarily an indication for surgery. Such local recurrence should be interpreted more as evidence of incomplete eradication of the slowly growing tumor rather than as manifestation of malignancy and an indication for surgery. In two of our successful cases, early recurrence of the tumor was detected bronchoscopically and treated by coagulation. The patients have been symptom-free for a period of ten and five years respectively (Table VI).

TABLE VI. DURATION OF SYMPTOM-FREE FOLLOW-UP PERIOD, BRONCHOSCOPY AND BIOPSY CONSISTENTLY NEGATIVE

RECURRENCE	NUMBER OF YEARS
	5
	14
	7
Local, in 1937, ----------	10
after 2 coagulations remained	2½
negative	5
	14
	1½
	10
	7
Local, in 1942, ----------	5
after coagulations remained	1
negative	4
	5
	10

It is imperative that all patients with adenoma be bronchoscoped occasionally so that biopsies can be taken of any suspicious areas, and the absence of tumor cells proved microscopically.

The patients have been followed from one to fourteen years. Many feel so well that they refuse to return for endoscopy. Only those who consistently return for observation are here included.

SUMMARY

Fifty cases of endoscopically proved adenoma of the bronchus are reviewed. Fifteen, or 30 per cent, of these remain completely cured or symptom-free following bronchoscopic removal, usually with coagulation of base.

Pedunculated smooth globular tumors originating in the main bronchi seem most suitable for endoscopic removal provided the diagnosis is established early. Tumors situated in the branch bronchi are distinctly not favorable, both because they are less accessible and show a tendency to spread intramurally.

In this series, the normal architecture of the bronchus was discernible after the fifth bronchoscopy. The persistence of the tumor as suggested by

bronchial wall involvement and proved by a consistently positive biopsy suggests extrabronchial spread and requires surgical removal. With the development of a relatively safe technique for the removal of a lung lobe, extrabronchial adenomas are now being treated in this manner with increasing frequency.

Unlike carcinoma of the bronchus, untreated patients with adenoma have a life expectancy of ten to twenty years. In an individual of advancing years, therefore, the need for lobectomy or pneumonectomy is not nearly as urgent as in instances of truly malignant neoplasms.

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CONTRALATERAL SPONTANEOUS PNEUMOTHORAX FOLLOWING LOBECTOMY

GEORGE E. GLEASON, M.D., ASPINWALL, PA., AND EDWARD M. KENT, M.D., PITTSBURGH, PA.

SERIOUS complications following pulmonary resection are becoming more and more infrequent with a resulting decrease in both morbidity and mortality which, in competent hands, predicts a safety of operation which will compare very favorably with any surgical procedure of parallel magnitude. Suppuration, bronchial fistula, and hemorrhage have been so reduced in importance as a complication after lobectomy or pneumonectomy that one actually encounters such setbacks but very rarely. However, unusual complications do occur from time to time and the recording of such an event is the purpose of this case report.

In brief, this an instance of persistent right spontaneous pneumothorax which occurred on the third day after the left lower lobe had been resected for bronchiectasis. The collapse of the right lung was complete, leaving virtually a single functioning pulmonary lobe, the remaining upper lobe on the left. Furthermore, the pneumothorax failed to respond to conservative measures and became so marked nineteen days after onset that right thoracotomy was necessary and the leaking emphysematous bleb was excised. Thereafter, recovery was rapid and complete.

CASE REPORT

D. L., a white man, aged 23 years, was admitted to the hospital on June 14, 1947, with complaints which included productive cough, anorexia, and loss of weight. The history indicated that the pulmonary complaints had followed a bilateral pneumonitis in 1942 for which he spent fifty-five days in an Army Hospital. In May, 1946, weight loss began and in October, 1946, the sputum became more abundant and fetid in odor. Upon admission the loss of weight had totaled fifty pounds in thirteen months. One month before entering the hospital he began to experience slight hemoptyses, chilliness, night sweats, and intermittent episodes of hyperpyrexia.

Clinical studies revealed that there were abnormal physical signs over the left lower chest most significant of which was the constant finding of râles upon auscultation. Further observations included a daily sputum production of 180 c.c. of thick, purulent secretion. Repeated examinations of this material were negative for acid-fast bacilli and cultures yielded a mixed flora. The intradermal tests with both strengths purified protein derivative were negative. A complete blood count indicated a moderate secondary anemia with a red cell count of 3,700,000 and a hemoglobin of 12 Gm., or 72 per cent.

Bronchography revealed bronchiectasis limited to the left lower lobe (Fig. 1). Bronchoscopy showed that a great deal of purulent secretion arose from the left lower lobe bronchus.

Preparatory therapy consisted of rest, sedation, high caloric intake, iron therapy, supplementary vitamin administration, postural drainage, and penicillin aerosol inhalations.

From the Thoracic Surgery Center, U. S. Veterans Administration Hospital, Aspinwall, Pa.
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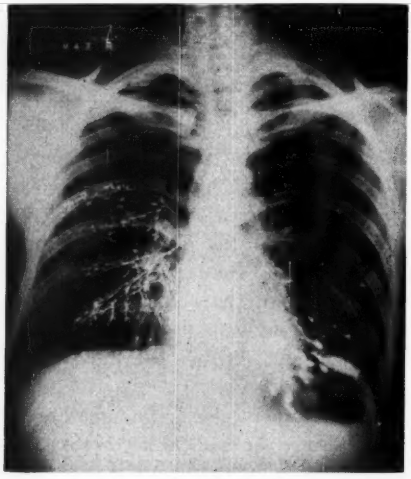

Fig. 1.

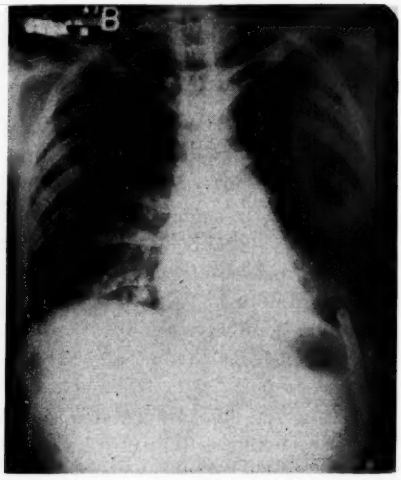

Fig. 2.

Fig. 1.—Bronchogram which reveals bronchiectasis of the left lower lobe.

Fig. 2.—Portable film of the chest taken Aug. 25, 1947, two days after resection of the left lower lobe.

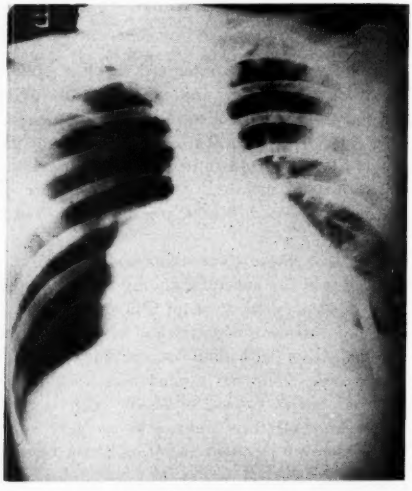

Fig. 3.—Portable film of the chest taken Aug. 29, 1947, on the third day after resection of the left lower lobe. There is a right spontaneous pneumothorax with complete collapse of the lung.

Clinical improvement followed this regimen and he was considered to have achieved maximum effect by Aug. 20, 1947. Consequently, left lower lobe resection was performed on Aug. 26, 1947, employing individual ligation technique for the vessels with careful closure and burial of the bronchial stump. The immediate postoperative course was uneventful and forty-eight hours after operation a chest x-ray film was taken as a routine matter (Fig. 2) whereby complete expansion of the remaining left upper lobe was established. During the following twelve hours the patient coughed a great deal and finally began to complain of moderate dyspnea. His color was good and the pulse rate was 104, however the respiratory rate was 35 per minute in an oxygen tent and a second bedside chest roentgenogram was taken (Fig. 3, Aug. 29, 1947), which revealed pneumothorax on the right side with complete collapse of the right lung.

Following this revelation 1,500 c.c. of air were aspirated from the right pleural space and eight hours later an additional 1,700 c.c. of air were removed. Expansion of the lung became complete within seventy-two hours. The patient was then permitted to follow a normal postoperative routine and was allowed out of bed on Sept. 4, 1947.

On Sept. 11, 1947, the right spontaneous pneumothorax recurred with complete collapse of the right lung as on the first occasion. Aspiration of 8,700 c.c. of air over a fifty-two hour period was followed by complete expansion of the lung. However, on Sept. 19, 1947, the spontaneous pneumothorax recurred once more and repeated aspirations of air totaling 22,500 c.c. over seven hours failed to expand the right lung. It was obvious that air was leaking into the pleural space as fast as it was being removed. Consequently, a right thoracotomy was performed at 6 P.M. on Sept. 19, 1947, twenty-three days after removal of the left lower lobe. The right lung was found to be completely collapsed. There was a cluster of six emphysematous blebs on the surface of the apex of the upper lobe, one of which was clearly shown to be leaking air continuously. This group of blebs was excised, the surface incision in the apex of the lung was repaired by suture, the lung was expanded, and the chest wound was closed. A single intercostal catheter was employed under water seal trap but this was removed after seventy-two hours.

The postoperative convalescence was rapid and uneventful. The patient was ambulatory on the fifth day after thoracotomy and was released from the hospital on the eighteenth day after operation. There has been no recurrence of spontaneous pneumothorax and he is free of the symptoms of bronchiectasis as well.

SUMMARY

1. A case history is presented which describes the occurrence of a right spontaneous pneumothorax on the third day after resection of the left lower lobe.

2. Despite the complete collapse of the right lung and the absence of the left lower lobe, the patient manifested only moderate dyspnea without cyanosis. The total functioning pulmonary area was confined to the single left upper lobe.

3. Tension pneumothorax with mediastinal shift to the opposite side did not occur. Had it been present, the respiratory embarrassment would undoubtedly have been much more marked.

4. Surgical intervention became necessary to control the right spontaneous pneumothorax which was found to be due to a leaking emphysematous bleb on the surface of the apex of the lung.

PRIMARY CHONDROSARCOMA OF THE LUNG

LAWRENCE M. LOWELL, M.D., AND JOHN E. TUHY, M.D.
PORTLAND, ORE.

CHONDROSARCOMA is a relatively uncommon tumor, and is exceedingly rare in the lung. In the case to be described the tumor appeared to be confined to the pulmonary artery and its branches. Compared to other reported chondrosarcomas it seemed to be unique in this respect.

CASE REPORT

History.—The patient, a 41-year-old white housewife, was first seen by one of us (J. E. T.) on Dec. 21, 1945. She had been well until June, 1944, when she noted the gradual onset of fatiguability, nervousness, anorexia, transient ankle edema, weight loss from 115 to 105 pounds, and dyspnea, tachycardia, and palpitation on moderate exertion. There was also a feeling of fullness and soreness in the left lower chest anterolaterally, made worse by exertion. Neither orthopnea nor nocturnal dyspnea was present. Examination by a physician in June, 1944, was said to have shown cardiac enlargement and a murmur. Rest was advised. She regained six pounds during August, 1944, but the complaints persisted. In September, 1945, she developed a nonproductive cough and symptoms of mild sinusitis. Early in November, 1945, she had a sudden attack of dyspnea on turning around quickly and was unconscious for five minutes. A week later there was a three-day episode of persistent nonpleuritic pain in the left lower chest posteriorly. At that time she began to lose weight again. The nonproductive cough persisted, and dyspnea and palpitation were present on slight exertion.

The patient had pneumonia in 1912 and 1913; an appendectomy and removal of a "tumor" of the left ovary in 1929; a spontaneous abortion in 1935 and a normal delivery in 1937; and pleurisy on the left side for one week in 1940. The last menstrual period was in September, 1945. Her father had had heart disease and her mother hypertension.

Physical Examination.—On Dec. 21, 1945, inspection revealed the patient to be pale, thin, and slightly dyspneic at rest. Pulse rate was 92, respiratory rate 30, blood pressure 136/64, temperature 98.6° F., and weight 103 pounds. The abnormal physical findings were limited to the cardiorespiratory system and consisted of: impaired resonance to percussion, weak breath sounds, and resonating râles after cough over the lower half of the left chest posteriorly; slight deviation of the heart and trachea to the left; very frequent extrasystoles; a loud pulmonic second sound; and a systolic murmur heard over each of the valve areas, that at the aortic area being transmitted into the neck. The neck veins were not distended, and no peripheral edema or liver enlargement was evident.

A roentgenogram of the chest made in June, 1944, showed some retraction of the heart to the left with prominence of the area of the pulmonary conus. There was a small density in the left lung adjacent to the mediastinum at the level of the left sixth posterior interspace. In December, 1945 (Fig. 1, *A*) this density was larger and there was a prominent mass posterior to the heart in the plane of the sixth to the ninth ribs posteriorly. The left leaf of the diaphragm was a little higher than the right, but the aeration of the left lung was good. The right lung appeared normal.

An electrocardiogram had been made on Dec. 11, 1945, by the referring physician.* He reported that it showed right axis deviation, a diphasic T wave in the second lead, and an isoelectric T wave in the precordial lead. Routine examination of the blood and urine was normal, and the blood Kahn reaction was negative.

From the Departments of Thoracic Surgery and Pathology, University of Oregon Medical School Hospitals and Clinics.

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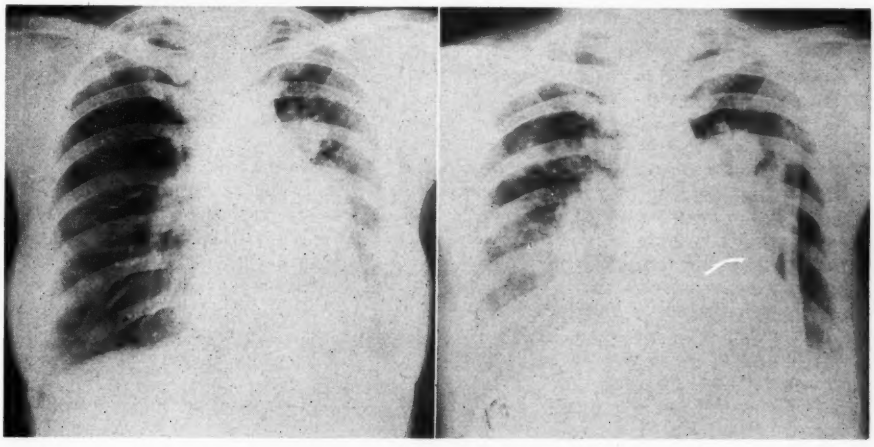
*Dr. Irvin Fox of Eugene, Oregon.

At bronchoscopy on Dec. 22, 1945, the left main stem bronchus and its devisions were seen to be displaced posteriorly as if by a mass lying anteriorly. No other abnormality was found.

It was concluded that the patient had a tumor of the left lung of undetermined type and a heart lesion of congenital or rheumatic origin. Because of the respiratory insufficiency, thoracoscopy following the institution of a left pneumothorax rather than an immediate exploratory thoracotomy was advised.

Clinical Course.—For various reasons the patient did not return for hospitalization until Feb. 17, 1946. Examination at this time revealed a rough presystolic and systolic mitral murmur transmitted to the left axilla. Systolic murmurs were also heard over the other valve areas. The liver margin was palpable 4 cm. below the right costal margin, and moderate persistent ankle edema was present. Fluoroscopy showed the densities near the left hilus to be somewhat larger. The right hilar shadow was enlarged and pulsated noticeably.



A. *B.*

Fig. 1.—*A*, Dec. 11, 1945, densities near the left hilus. Shift of the heart to left with prominence in area of the pulmonary conus.

B, Feb. 21, 1946, bilateral hilar densities and infiltration in the right second anterior interspace; artificial pneumothorax, left.

In twenty-four hours she produced 15 c.c. of mucopurulent sputum which was negative for tubercle bacilli on concentration. The voided urine contained 130 mg. per cent albumin, occasional hyaline and many granular casts, a few erythrocytes, and many leucocytes per high-power field. A routine blood count and sedimentation rate were within normal limits.

Digitalization was begun on February 18 because of apparent right heart failure. Left pneumothorax was instituted on the same day. Eight hours later she became quite dyspneic and cyanotic, and air was withdrawn once. Fluoroscopy next day revealed a 20 per cent collapse of the left lung with apical adhesions. Small pneumothorax refills were given on February 19 and 20. Oxygen therapy was given intermittently because of dyspnea. A roentgenogram of the chest taken on February 21 showed considerable increase in the right hilar shadow with a fuzzy area of infiltration 2 cm. in diameter in the right upper lung field. The densities near the left hilus were larger than in the previous films. A 20 per cent collapse of the lower two-thirds of the left lung was present (Fig. 1, *B*).

It was decided to forego thoracoscopy and to abandon the pneumothorax because of the patient's poor condition and because it was feared that the tumor might already have metastasized to the right lung. After 350 c.c. of air had been aspirated from the left pleural cavity

on February 25 she become more cyanotic and dyspneic. Six hours later signs of marked peripheral vascular collapse were present. Oxygen therapy and plasma given intravenously were of temporary benefit only, and she died the same day.

Pertinent Gross Autopsy Findings (Fig. 2).—The heart, which weighed 420 grams, showed moderate dilatation of the right atrium and ventricle with hypertrophy of the latter. No gross valvular changes were present. A tumor in the pulmonary artery extended to within 1 cm. of the pulmonary valve, where together with a small thrombus it completely occluded the vessel. The wall of the pulmonary artery contained a few small arteriosclerotic plaques, and there was moderate thickening of its intima.

Posteriorly at the level of the left fifth rib the parietal and visceral pleural surfaces were fused. A few easily separated adhesions were present over other areas of both lungs. Approximately 200 c.c. of clear pink fluid and an estimated 200 c.c. of air were present in the left pleural cavity. The left lung weighed 540 grams and the right lung 750 grams. The left lung was small and firm. On the medial surface of the left lung below the hilus a white tumor was seen through the pleura. A frontal section through the left lung revealed, near the hilus, a firm white tumor mass measuring 6 by 10 cm. This mass extended into and almost filled the left pulmonary artery, the main pulmonary artery, the primary branches of the right pulmonary artery, and the smaller branches to the right apex. Within the left lung the growth was lobulated and in most places it was sharply demarcated from the compressed reddish-brown lung. The tumor was firm and grated slightly when cut. For the most part it was definitely bounded by arterial walls, and dissected portions of the tumor resembled casts of small branching blood vessels. No connection was found between the intra-arterial tumor and any bronchus, although the left lower lobe bronchus was moderately distorted and compressed. Within the main pulmonary artery the tumor was soft, friable, and fungating. No gross changes were noted in the hilar or mediastinal lymph nodes, except for two glands in the right hilus which had undergone calcification. The right lung was crepitant and appeared normal externally. On section there was tumor involvement in the upper portion as described previously.

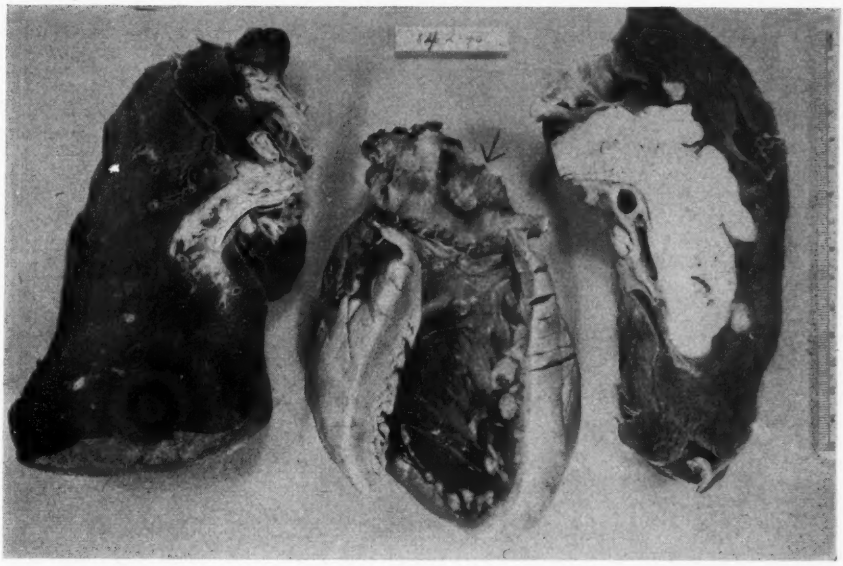
The liver weighed 1,330 grams and showed changes typical of chronic passive hyperemia. Examination of the other organs and of the bones and joints revealed no evidence of primary or metastatic malignancy.

Histopathology.—The portion of the tumor within the main pulmonary artery resembled adult cartilage (Fig. 3, *A*), except that calcification and necrosis were widespread, and there was increased cellularity with plump and occasionally double nuclei. Sections from the tumor extended to the right apex (Fig. 3, *B*), however, revealed cartilaginous islands in a stroma of undifferentiated mesenchymal cells with pale-staining cytoplasm, and nuclei which were round, oval, or occasionally spindle-shaped. Areas of necrosis and myxomatous degeneration were widespread. The least differentiated portions (Fig. 3, *C*) were found within the main tumor mass in the left lung where there was no resemblance to cartilage. The cells here had much larger nuclei, moderately hyperchromatic and often spindle-shaped, but only an occasional mitotic figure was present.

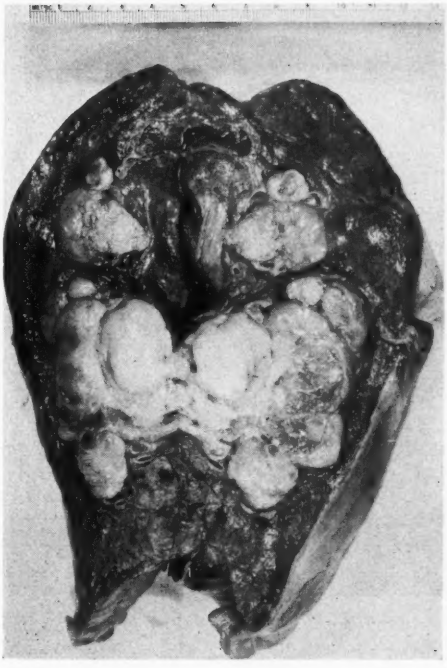
In one section several small spicules of bone not associated with cartilage were seen in the malignant-appearing stroma. Many vascular channels lined with either endothelial or tumor cells were present. For the most part the tumor was bounded by arterial wall (Fig. 3, *D*); in other places the boundary was too thin to identify it as such. No clefts lined with epithelium, commonly seen in hamartomas of the lung,[2] were seen. Wilder's silver stain revealed a fine reticulum throughout the less differentiated portions of the tumor. A whorl-like arrangement of the cells was demonstrated, and tortuous lymph or blood vascular channels were sharply outlined.

Changes in the left lung outside of the tumor consisted of patchy atelectasis, chronic passive hyperemia, and edema. Apart from the neoplasm no significant pathology was found in the right lung.

The liver displayed the moderate central lobule necrosis of passive hyperemia. The microscopic findings in the remainder of the organs were normal or noncontributory to this report.



A.



B.

Fig. 2.—*A*, frontal sections through both lungs; heart with right ventricle and pulmonary artery opened to expose tumor (arrow). Note that the tumor follows distribution of pulmonary arteries. *B*, Section through unfixed left lung showing bulging chondrosarcomatous masses.

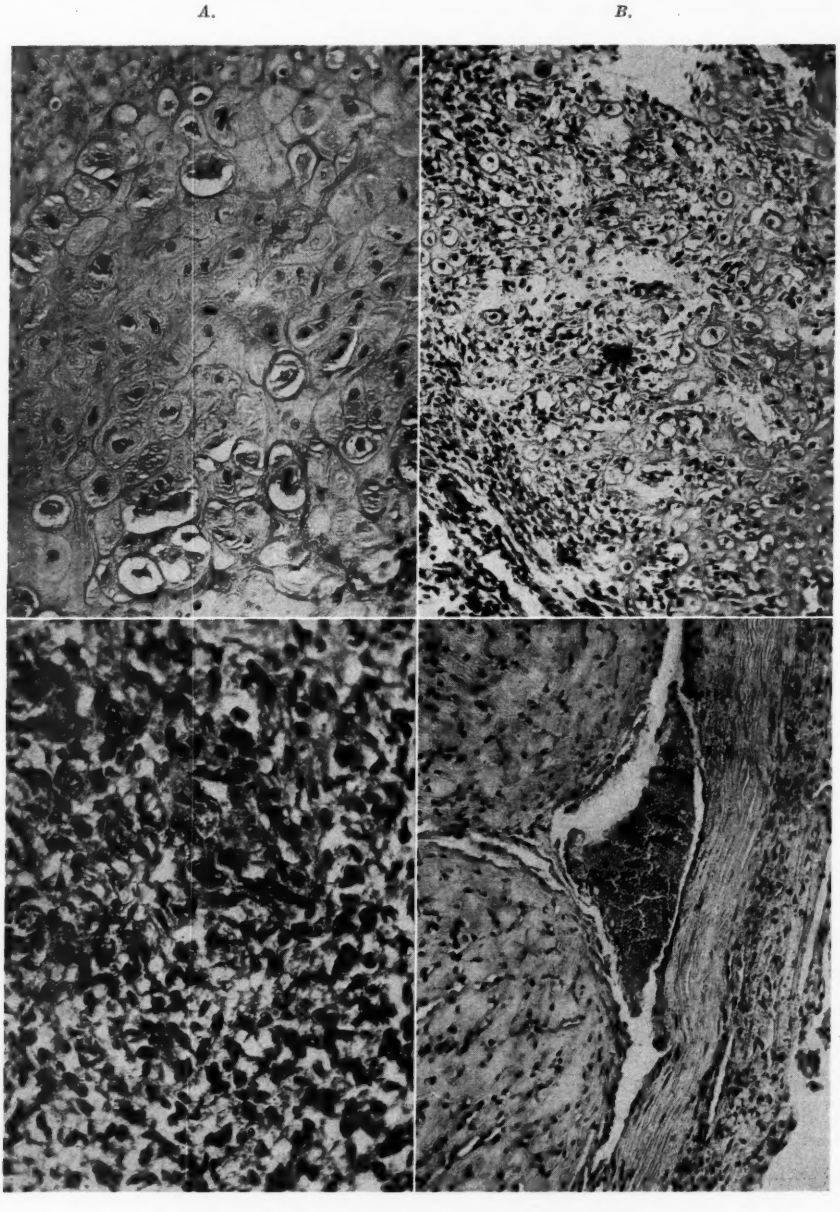


Fig. 3.—Photomicrographs of tumor. *A*, Within main pulmonary artery (×130); here the chondrosarcoma is well differentiated. *B*, Within branch of pulmonary artery to right apex (×130); both differentiated and undifferentiated chondromatous cells are seen in this field. *C*, From main tumor mass in left lung (×275); only chondroblasts occur here. *D*, Section through pulmonary artery containing tumor and thrombus (×130).

DISCUSSION

Greenspan[1] in 1933 reported a case of "primary osteoid chondrosarcoma" of the lung, which he believed to be the first reported in the literature, although he stated that a case reported by Roe[3] in 1866 had similar gross anatomic characteristics. Greenspan was able to demonstrate marked narrowing of the lumen of a bronchus and infiltration of its wall by tumor tissue. He described osteoid elements in the tumor and metastatic tumor nodules in the pericardium, pleurae, and myocardium. None of these features was present in our case, in which the tumor seemed to be limited to the pulmonary artery and its branches. The following points of similarity do exist: (1) invasion of the pulmonary artery producing cor pulmonale, (2) similarity in gross appearance, (3) pleomorphism evident microscopically, (4) no clinical or autopsy evidence of a primary source of a neoplasm outside the lung, and (5) absence of metastases outside the thorax.

Greenspan's case obviously can be regarded as malignant and therefore as a chondrosarcoma, rather than as a benign chondroma, simply on the basis of the demonstrable metastases. The case herewith reported exhibited gross malignant characteristics only by its having advanced through the pulmonary arterial system, no discontinuous metastases having occurred. It would therefore seem advisable to support the diagnosis of malignancy by histopathologic evidence. In 1940 Ewing[4] stated that "while in general the more cellular and softer tumors, as myxochondroma, are the more malignant, both clinical and histological features should be regarded in applying the term chondrosarcoma." Lichenstein and Jaffe[5] in 1943 presented the first satisfactory study of the transition stages between benign and malignant cartilage tumors based on histologic features alone. It is true that their study dealt only with cartilage tumors arising from cartilaginous elements of bone; however, it seems logical to apply the same criteria in judging the malignancy of any cartilage tumor.

Lichenstein and Jaffe stated that "a cartilaginous tumor should no longer be regarded as benign if, when viable and not heavily non-calcified areas are examined, it shows, even in scattered fields: (1) many cells with plump nuclei, (2) any giant cartilage cells with large single or multiple nuclei or with clumps of chromatin." The microscopic examination in our case fulfills these criteria. In addition pleomorphism was marked, the cellular picture ranging from completely undifferentiated spindle-shaped cells to mature cartilage cells. In fact, the tumor affords an excellent study of the histogenesis of cartilage, exhibiting as it does all phases of cartilage formation.

Greenspan's case of chondrosarcoma primary in the lung was the only one which could be found in the literature. However, reports of nineteen cases of chondrosarcoma arising in a distant bone and metastasizing to the lung were collected by Castren[6] in 1931. In several of these there was uninterrupted extension from an obvious primary site through the inferior vena cava, heart, and pulmonary arteries.[4, 6] Grossly and histologically the pulmonary metastases in this latter group were quite similar to the primary tumor reported in this paper. Chondrosarcomas may arise from the ribs and sternum but rarely invade the lung secondarily.

Six cases of primary sarcoma of the pulmonary artery with metastases to the heart and lungs were collected recently by Durgin and Ingleby.[7] However, all these tumors appeared to arise from the intima or muscularis, and none was cartilaginous.

At least ninety-six primary benign cartilage tumors,[2] usually designated as "hamartomas" in the recent literature, have been reported. They represent overgrowths of the epithelial and mesothelial elements normally found in bronchi, the epithelial component appearing as clefts lined with epithelium (usually ciliated), the mesothelial element as adult cartilage. None of these tumors has been noted within pulmonary vessels.

Simon and Ballon[8] recently reported an unusual case of hamartoma of the lung which showed microscopic evidences of malignancy much like those described in our case, although there were no metastases and no invasion of pulmonary vessels. This tumor, unlike ours, contained definite clefts lined with epithelium, a fact which makes its origin from a hamartoma quite likely.

We are at a loss to account for the exact origin of the tumor described in this communication. It may have arisen in a bronchus and then invaded the pulmonary arterial system, as did the tumor reported by Greenspan, although such a sequence could not be verified by careful dissection or by study of the microsections. Only one adequately described hamartoma showing definite malignant characteristics has so far been reported.[8] The rarity of such a picture together with the absence of epithelial clefts in our tumor are strongly against its development from a hamartoma. If it arose from a distant chondrosarcoma of bone which was overlooked at autopsy, it would still be without precedent, since such previously reported tumors all showed an obvious primary site. It also seems farfetched to postulate an origin in the wall of the pulmonary artery.

Clinical Comment.—The onset of this patient's signs and symptoms occurred about twenty months before death. Presumably the tumor first gradually filled the left pulmonary artery causing right axis deviation and a loud pulmonic second sound. The roentgenograms suggest that the spread to the right pulmonary vessels occurred only in the last month or two of life, at which time the right heart strain rapidly became more pronounced. Right heart failure was well marked in the last week, and the terminal event was thrombosis in the remaining lumen of the main pulmonary artery.

The presence of a tumor within the pulmonary vessels is seldom suspected during life because of the rarity of such an occurrence. The inclination is to attribute the cardiac signs and symptoms to the familiar effects resulting from myocardial or valvular disease. It is doubtful if a tumor in the pulmonary artery large enough to produce cardiac strain would be amenable to surgical removal.

SUMMARY

A unique case of primary chondrosarcoma in the lung filling both pulmonary arteries is reported. A discussion of the factors concerned in the pathologic diagnosis is given, and the literature relating to cartilage tumors involving the lung is briefly reviewed.

The advice of Dr. Vinton D. Sneeden and Dr. Warren C. Hunter of the Department of Pathology and of Dr. William S. Conklin of the Division of Thoracic Surgery of the University of Oregon Medical School is gratefully acknowledged.

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LOBECTOMY IN COCCIDIOIDOMYCOSIS

Report of Two Cases

Julian A. Moore, M.D., Asheville, N. C., James D. Murphy, M.D., Oteen, N. C. and D. E. Ward, Jr., M.D., Winston-Salem, N. C.

SINCE the advent of World War II, coccidioidomycosis has been seen in all sections of the country. The high incidence of this infection is due to the fact that during the war many service men were stationed in or traveled through endemic areas of coccidioidomycosis in the San Joaquin Valley, central and other parts of California, Arizona, and Texas. These men were exposed to the chlamydospores of *Coccidioides immitis*. Many contracted the disease and were treated, while others had asymptomatic primary disease and were not treated. Patients in this latter classification are now being admitted with secondary coccidioidal cavities. This paper contains reports of two such cases which we would like to discuss briefly.

In reviewing the literature, we were able to find reports of only two cases of coccidioidomycosis in which lobectomy was done. Peers, Holman, and Smith[1] reported a case in 1942 in which a right upper lobectomy was performed for a solitary cavity. Their indication for surgery was fear that the patient was in danger of dissemination of the infection throughout the rest of the body. Pneumothorax was tried first, but this did not close the cavity and sputum and gastric washings remained positive for *Coccidioides immitis*. A right upper lobectomy was then done, followed by a thoracoplasty.

The second case was reported to one of us (J. A. M.) by Blades of Washington, D. C.[2] Blades did a lobectomy at Walter Reed Hospital for a single large cavity in the left upper lobe which had been present for two years. The indication in this case was hemoptysis. An excellent result was obtained.

CASE REPORTS

Case 1.—H. W., a 25-year-old Negro man served in the army from Jan. 21, 1943, until Jan. 13, 1946. During part of this service he was stationed in the desert area of California, but did not manifest any symptoms of coccidioidomycosis at any time while in the army.

At the separation center, Camp Blanding, Florida, roentgenologic examination Jan. 13, 1946, revealed a cavity in the lower lobe of the right lung, although he had had no previous symptoms (see Fig. 1). A diagnosis of "tuberculosis, pulmonary, chronic, moderately advanced, active" was made and the patient was transferred to Moore General Hospital, Swannanoa, N. C., March 7, 1946, for treatment.

On admission he was asymptomatic, had a good appetite, and had lost no weight. On physical examination he appeared well developed, well nourished, and did not seem acutely or chronically ill. Examination of the lungs was negative. No râles were present. Temperature was normal, blood pressure was 110 systolic, 65 diastolic, and pulse 78 per minute. There was no familial history of tuberculosis.

From the Department of Medicine and Surgery, Veterans Administration Hospital, Oteen, North Carolina; published with permission of the Chief Medical Officer, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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Laboratory findings on admission were as follows: total erythrocyte count 4,780,000, hemoglobin 91 per cent, total leucocyte count 8,700, with 50 polymorphonuclears, 38 lymphocytes, 8 monocytes, 3 eosinophiles, and 1 basophile. The blood sedimentation rate (Wintrobe, corrected) was 7 mm. per hour. Urinalysis showed acid reaction, specific gravity 1.018, negative for albumin and sugar, and negative on microscopic examination. The vital capacity was 3,500 cubic centimeters. Serology (Kahn) was negative. Seven direct sputum smears, four seventy two-hour sputum concentrates, two sputum cultures, and a guinea pig inoculation were negative for acid-fast bacilli.

Bronchoscopies on June 24, 1946, Aug. 13, 1946, and Jan. 31, 1947, were negative and cultures taken for acid-fast bacilli and *Coccidioides immitis* were negative. He had a positive (+15) skin test for tuberculosis in the first strength, Coccidioides skin test was negative in the 1:1,000 dilution and positive (+10) in the 1:10 dilution. Histoplasmosis skin test was negative in the 1:1,000 dilution and positive (+5) in the 1:10 dilution.

In June, 1946, blood was sent to the Stanford University School of Medicine for serological test for coccidioidomycosis. Complement fixation tests were reported as negative.

The cavity in the right lower lobe increased in size (Fig. 2) four and one-half months after admission. There was no infiltration around the cavity. The left lung was clear. Lipiodol studies revealed only one cavity present in the right lower lobe.

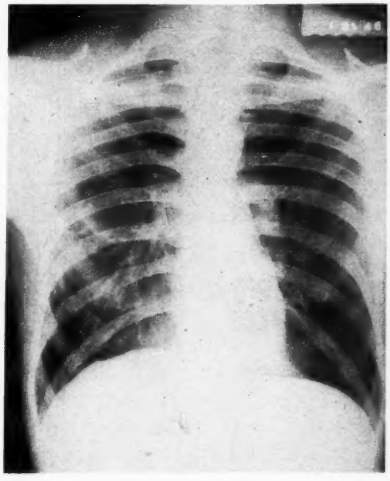

Fig. 1.

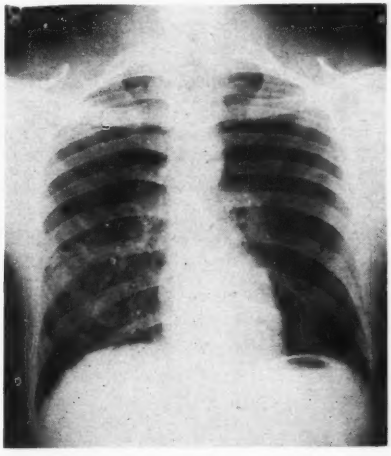

Fig. 2.

Fig. 1 (Case 1).—X-ray film taken Jan. 31, 1946, at separation center, Camp Blanding, Fla., showing single thin-walled cavity in upper portion of right lower lobe. Note absence of other pulmonary disease.

Fig. 2 (Case 1).—X-ray film taken June 14, 1946, at Moore General Hospital, Swannanoa, N. C., showing increase in size of cavity in right lower lobe during four and one-half months of bed rest.

A right phreniclasia was done Feb. 13, 1947, in order to collapse the cavity but no decrease in size was noted. In view of the negative tuberculin findings, a diagnosis of lung cyst, right lower lobe, was made and the patient was transferred to the Veterans Administration Hospital at Oteen, N. C., April 7, 1947, for surgery.

At this time his only complaint was occasional pain in the right posterior chest on deep breathing. He was afebrile and his weight remained at a constant level. On April 4, 16, 22, and 24 (fifteen months after the cavity was discovered) his sputum was positive by smear and culture for *Coccidioides immitis*. X-ray examination now revealed a thin-walled cavity in the posterior portion of the right upper lobe near the apex. In view of the positive

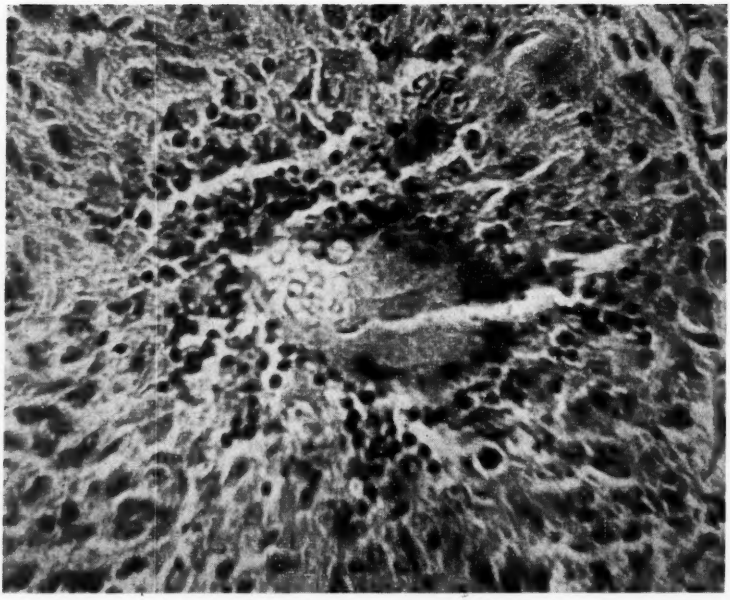

Fig. 3 (Case 1).—Photomicrograph illustrating a round spherule filled with endospores found in cyst wall.

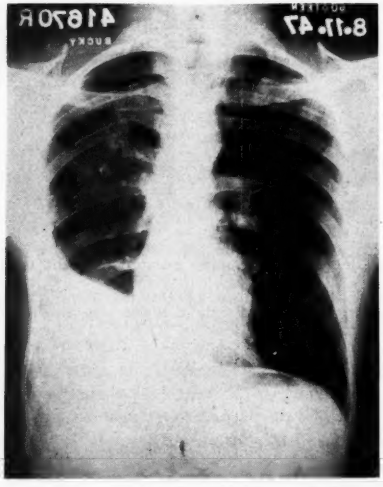

Fig. 4 (Case 1).—X-ray film taken Aug. 8, 1947, at Veterans Administration Hospital, Oteen, N. C., three months after right lower lobectomy. Note degree of expansion of middle lobe.

Coccidioides culture, the condition was diagnosed as coccidioidomycosis with cavitation. Apparently we were dealing with a residual cavity from a prior attack of primary coccidioidomycosis which was asymptomatic.

May 8, 1947, under cyclopropane and ethylene anesthesia a right lower lobectomy was performed. The patient was given 1,000 c.c. of whole blood and 1,300 c.c. of a 5 per cent solution of glucose in saline during the operation. A 2.5 cm. thin-walled cavity was found in the right upper lobe. On microscopic examination the wall of this cavity was seen to consist of a caseous mass supported by granulation tissue made up of capillaries, plasma cells, eosinophiles, and polymorphonuclear leucocytes. In the granulation zone was a slightly distorted, pale-blue staining spherule filled with endospores (Fig. 3). Giant cells in a few instances contained one or several spherules. In the adjoining lung tissue numerous structures resembling epitheloid cell tubercles were seen. The microscopic diagnosis was coccidioidomycosis of the lower lobe of the right lung, granulomatous and cavity-forming.

The postoperative course was uneventful except for a hydrothorax which was aspirated once on May 15, 1947. Seven hundred cubic centimeters of serosanguineous fluid were removed and were found negative for *Coccidioides immitis*. The sputum remained positive on smear, concentrate, and culture for spherules. In an effort to find the source of the positive sputum, planigrams of both lung fields were made but these revealed no further evidence of cavitation. Bronchoscopy on July 8, 1947, showed reddening of the right middle orifice but no signs of endobronchial disease. Bronchoscopy on July 29, 1947, was negative.

Potassium iodide and sulfadiazine were given for one week followed by a therapeutic intratracheal instillation of iodized oil on Aug. 21, 1947. The sputum turned negative on concentrate but remained positive on culture for spherules of *Coccidioides immitis*.

X-ray examination Aug. 8, 1947, showed re-expansion of the upper and middle lobes of the right lung (see Fig. 4). The patient was asymptomatic and was gaining weight. He was discharged Aug. 30, 1947, three months and twenty-three days after lobectomy.

He returned to the hospital for a check-up examination Dec. 15, 1947. At this time he was asymptomatic and working regularly. The sputum examinations (smear and culture) March 3, 1948, were negative for *Coccidioides immitis*.

Comment.—This case illustrates the innocent roentgenographic appearance and innocuous behavior of cavitation following primary quiescent coccidioidomycosis. Undoubtedly this patient had a primary infection during military service which was asymptomatic. At separation center his residual cavity was discovered. The condition was diagnosed as pulmonary tuberculosis, a common error in these cases. When no acid-fast bacilli could be found on repeated and extensive study, the condition was then diagnosed as cyst of the lung. A positive sputum for *Coccidioides immitis* was not obtained until fifteen months after the cavity was discovered. The difficulty of making the correct diagnosis is clearly demonstrated by this case.

The symptom of posterior chest pain over the cavity is a common finding in residual pulmonary cavities. The usual symptoms of fever and loss of weight were not present. An important observation is the increase in the size of the cavity (Figs. 1 and 2) during the four and one-half months of bed rest. The cavity remained large, as Fig. 2 indicates, until lobectomy eleven months later.

At first a phreniclasia was done in an attempt to close the cavity, but this was unsuccessful. When cavities are large, phreniclasia is usually of no value. In view of the persistence of the cavity and the danger of dissemination or hemoptysis, a lobectomy was considered the treatment of choice in this case. Following lobectomy the sputum remained positive, although planigrams of

both lung fields and bronchoscopy revealed no further evidence of disease. A positive sputum does not constitute a public health menace, for coccidioidomycosis is produced by the chlamydospores of the fungus which are contacted from the environment in endemic areas. Infection does not pass from person to person via sputum containing endospores or spherules.[6] Unlike tuberculosis, the spherule does not lend itself to dissemination of the fungus outside the animal body.

At the time of discharge this patient was asymptomatic and gaining weight. He returned to his occupation as waiter. On follow-up examination six months after discharge he was still symptom free and sputum was negative. In this case we feel that lobectomy provided the most effective method of treatment.

CASE 2.—B. S., a 25-year-old white man, served in the army from Jan. 16, 1944, until March 26, 1946. Part of the time he was stationed in Texas, Arizona, California, and the European theater. While in the army he had no symptoms of coccidioidomycosis or any related disease.

During the summer of 1946 (three months after discharge) he first noticed that he felt unusually weak, tired easily, and was losing weight. He developed a cough which was productive of a moderate amount of grayish-brown sputum and complained of soreness and pain beneath his sternum. He paid little attention to these symptoms, however, and continued working as a mechanic in a garage. Symptoms persisted, and in November, 1946, he first observed blood-streaked sputum. There was never any hemorrhage but he coughed up as much as a tablespoonful of blood at a time. This condition did not improve. In December, 1946, he went to his local physician for the first time. Upon roentgenologic examination a large cavity was discovered in the upper lobe of the left lung with no involvement of the right lung (see Fig. 5).

On Jan. 8, 1947, he was admitted to the Veterans Administration Hospital, Swannanoa, N. C. Chief symptoms were cough, blood-streaked sputum, and a weight loss of thirty pounds even though the appetite remained good. At this time he complained of pains "between the shoulder blades and severe left chest aching" at night. Physical examination revealed a well-developed, well-nourished white man who did not appear acutely or chronically ill. Examination of the lungs showed coarse breath sounds over the left apex posteriorly. No râles were present. Temperature was 99° F.; the blood pressure was 140 systolic, 80 diastolic, and pulse 80 per minute. The remainder of the physical examination was essentially negative.

Laboratory Findings.—On admission the total erythrocyte count was 4,930,000, hemoglobin 94 per cent, and the total leucocyte count 7,950 with 61 per cent polymorphonuclears, 34 per cent lymphocytes, with 4 per cent monocytes and 1 per cent basophiles. The erythrocyte sedimentation rate (Wintrobe, corrected) was 6 mm. per hour. Urinalysis revealed amber color, acid reaction, a specific gravity of 1.024, negative for sugar and albumin, and a few white blood cells on microscopic examination. Serology (Kahn and Kolmer) was negative. The total serum protein was 7.1 Gm. per cent with albumin 4.6 and globulin 2.5 Gm. per cent. The coccidioidin skin test was positive (30 mm.) 1:1,000 dilution. Tuberculin skin test (0.05 mg., purified protein derivative) was positive (10 mm.). Histoplasmin skin test was negative in 1:1,000 and 1:10 dilutions. All sputum smears, concentrates, and guinea pig inoculations were negative for acid-fast bacilli. Bronchoscopy on Feb. 17, 1947, revealed a minimal amount of blood seen at the left main-stem bronchus. Smear and culture were negative for acid-fast bacilli but a positive culture of *Coccidioides immitis* was found.

Planigrams on Feb. 28, 1947, revealed a mottled infiltration and a thin-walled cavity in the upper lobe of the left lung. March 7, 1947, a left bronchogram was done and iodized oil filled the cavity (see Fig. 6).

A diagnosis of pulmonary coccidioidomycosis with cavitation in the left upper lobe was made and the patient transferred to the Veterans Administration Hospital, Oteen, N. C.,

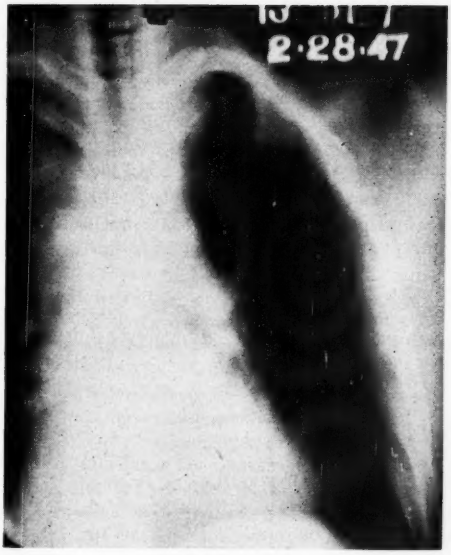

Fig. 5.

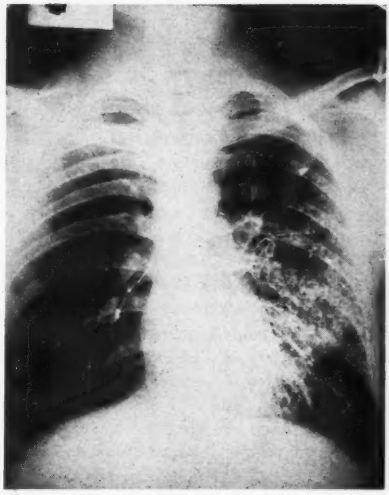

Fig. 6.

Fig. 5 (Case 2).—Planigram taken Feb. 28, 1947, an Swannanoa Division of Veterans Administration Hospital, Oteen, N. C., showing solitary thin-walled cyst (under fourth rib) in left upper lobe.

Fig. 6 (Case 2).—Bronchogram taken March 7, 1947, at Swannanoa Division of Veterans Administration Hospital, Oteen, N. C., demonstrating size of the cavity (between fourth and fifth ribs) by Lipiodol.

Fig. 7.

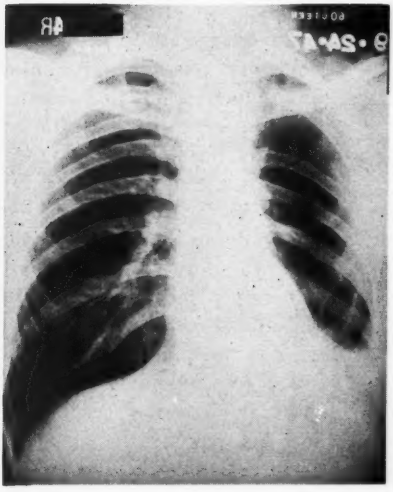

Fig. 8.

Fig. 7 (Case 2).—Photomicrograph illustrating spherules of *Coccidioides immitis* within giant cells. Note chronic granulation tissue.

Fig. 8 (Case 2).—X-ray film taken Sept. 24, 1947, at Veterans Administration Hospital, Oteen, N. C., showing expanded lower lobe three months, eighteen days following left upper lobectomy.

on April 1, 1947. He still complained of pain in the left chest and cough which was productive of blood-streaked sputum. Blood count, urinalysis, and serology were negative. The vital capacity was 5,200 c.c. (normal: 5,050 c.c.). Sputum smears, concentrates, and cultures for acid-fast bacilli were negative. Spherules of *Coccidioides immitis* were found in the sputum on April 2 and April 4, and cultures were positive for *Coccidioides immitis*. The erythrocyte sedimentation rate was 2 mm. per hour (Wintrobe, corrected).

Planigrams on April 10, 1947, again demonstrated the cavity in the left infraclavicular region. The right lung remained clear. The electrocardiographic tracing was normal.

A diagnosis of coccidioidomycosis with cavitation in the left upper lobe was made and the therapy conference board recommended left upper lobectomy, which was performed May 6, 1947, under cyclopropane and ethylene anesthesia. During the operation he received 1,000 c.c. of whole blood, 1,000 c.c. of plasma, and 1,000 c.c. of a 5 per cent solution of glucose in normal saline solution.

The pathologist reported a 2.2 by 1.1 cm. cavity in the left upper lobe. On microscopic section the lesions everywhere resembled those found in tuberculosis, except for fine histologic detail. Spherules of *Coccidioides immitis* were found within giant cells or free in tubercles (see Fig. 7). Surrounding the tubercles and elsewhere was chronic nonspecific granulation tissue and fibrosis. Part of the peribronchial lymph nodes showed preserved follicular structure, but in other sections there were epitheloid cell tubercles and giant cells undergoing caseation. The final diagnosis was coccidioidomycosis of the upper lobe of the left lung, granulomatous and cavity-forming, involving peribronchial lymph node.

The entire postoperative course was uneventful and the remainder of the lung gradually re-expanded. This patient was discharged asymptomatic May 29, 1947 (twenty-three days following lobectomy). A follow-up x-ray film on Sept. 24, 1947, three months, eighteen days after operation, showed the remainder of the left lobe fully expanded (Fig. 8). This patient had no complaints and was working every day with no ill effect.

Comment.—This case also illustrates the asymptomatic character of primary coccidioidomycosis with pulmonary cavitation as a residual complication. This patient served in endemic coccidioidal areas but was never ill. Three months after discharge he noticed the first symptoms: weakness, loss of weight, and cough productive of grayish-white sputum—symptoms similar to those of tuberculosis with which coccidioidomycosis is often confused. Later hemoptysis (but not hemorrhage) and chest pain were noted, symptoms characteristic of residual coccidioidal cavities.

The erythrocyte sedimentation rate and other laboratory data were essentially negative. Both the tuberculin and the coccidioidal skin tests were positive, a common finding in coccidioidal infection. *Coccidioides immitis* was found in the sputum nine months after symptoms were first noted.

Judging from our previous experience with phreniclasia, it was felt that this procedure would not close the cavity, especially since it was located in the left upper lobe. In view of the large size of the cavity, lobectomy was considered the treatment of choice. The sputum was negative following surgery and the patient was discharged twenty-three days after operation. When seen nine months after discharge, he was still asymptomatic and working daily at his former occupation. In this instance lobectomy achieved a gratifying end result.

DISCUSSION

In the past it has been the general consensus of opinion that pulmonary cavitation following coccidioidomycosis should be treated conservatively. In

1942 Winn[4] reported twelve cases of pulmonary cavitation treated from four months to four years under normal and unrestricted living and working conditions without collapse therapy. In five, the cavities closed spontaneously; in the remaining seven, the cavities remained with little change in roentgenographic appearance and without evidence of dissemination. In two cases Winn employed pneumothorax successfully for excessive bleeding. Two other patients had open cavities six months and two and one-half years after pneumothorax treatment. Both cavities closed after the lung was re-expanded. Winn concluded that persistent pulmonary hemorrhage or the occasional large cavity associated with the continuous production of spherule-laden sputum may be an indication for simple collapse measures.

Denenholz,[5] in 1944, reported a series of five patients with pulmonary cavities which were treated by bed rest and the application of a cloth bag containing lead shot over the anterior aspect of the portion of the chest involved. The weight applied began at three pounds (1.5 kg.) and gradually was increased to eight pounds (3.6 kg.). He believed that cavities closed more rapidly on this method of treatment than with bed rest alone. He did not employ pneumothorax in any of his cases. Phreniclasia was used in two cases to reduce the size of the cavity. Denenholz also mentioned immobilization with a lead shot bag as of some benefit in helping to close thin-walled cavities.

Thus, there are many opinions as to the method of treatment of pulmonary cavitation in coccidioidomycosis. In some instances the patients have continued to work and the cavities have closed without any treatment. Rest in bed has been successful in other instances. Phreniclasia and immobilization with lead shot bag have been used as an adjunct to bed rest. Lobectomy has been employed in two previous cases and here at Oteen in two cases. We should like to emphasize the importance of lobectomy for patients with residual thin-walled cavities.

Two main dangers must be faced in any patient with a residual pulmonary cavity from coccidioidomycosis. The first is the possibility of dissemination of the pulmonary disease to other parts of the body. Denenholz[5] stated that the mortality is greater than 50 per cent in disseminated coccidioidomycosis, although dissemination rarely occurs. Quill and Burch[7] reported four cases of disseminated coccidioidomycosis in 1944. Two of the patients died in two months and the other two in four months, a mortality of 100 per cent. Dissemination is definitely a serious and usually fatal sequela in any patient with a pulmonary cavity.

The second danger is hemoptysis. It is generally agreed that patients who have had one or more pulmonary hemorrhages from their cavity should have immediate and adequate therapy to stop the hemoptysis. Pneumothorax has been tried in some cases as reported by Peers, Holman and Smith[1] but without success. Phreniclasia has been tried, as in our first case, without success. Hemoptysis is a distressing symptom and if unchecked is usually fatal.

Lobectomy definitely appears the most practical and efficient method of treatment for a patient with a residual cavity from primary coccidioidomycosis.

Excision of the diseased lobe averts all risk of dissemination and hemoptysis. The patient is then free of his disease and will not live in constant fear of the development of a fatal complication. Also, he will be relieved of the symptom of pain in the chest, a common symptom and one exhibited by both of our patients.

We realize that lobectomy is a new and different form of therapy for residual coccidioidal cavitation but believe that the nature and complications of the disease warrant immediate and extensive treatment. The results in our two patients, as reported above, seem to justify the employment of this procedure. Time and the end results in similar cases may afford the answer to the problem.

SUMMARY

1. The literature on the treatment of pulmonary cavitation in coccidioidomycosis has been briefly reviewed.

2. Two cases of residual pulmonary cavitation following primary coccidioidomycosis are reported, both successfully treated by lobectomy.

3. Lobectomy is recommended as an effective and practical method of treatment in similar cases.

ADDENDUM

CASE 2.—B. S. was readmitted Aug. 30, 1948, complaining of severe nonproductive cough, weakness, and night sweats. X-ray examination showed a thin-walled cavity 4 cm. in diameter in the upper portion of the remaining left lower lobe. Surrounding the cavity were productive strands and small areas of exudative disease. The sputum was positive for acid-fast bacilli. Coccidioidin skin test was negative in the 1:1000 and 1:100 dilution on Sept. 7, 1948. On Jan. 10, 1949, it was reported positive in dilution of 1:1000. Culture of the sputum was negative for coccidioides.

A seven-rib left thoracoplasty was completed Nov. 17, 1948. The surgical collapse had little effect on the cavity, which remained thin-walled and with a diameter of 3 cm. An open cavernostomy was completed on March 3, 1949. Smears from the cavity wall showed coccidioidal spherules, as did tissue sections. Culture of the material from the cavity was positive for tubercle bacilli.

The patient remains in the hospital. The cavernostomy has not completely obliterated the cavity. The course following the original lobectomy has not confirmed our early optimism.

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CARCINOMA OF THE ESOPHAGUS

Use of Rigid Indwelling Esophageal Tube

A. L. Brown, M.D.
San Francisco, Calif.

A HIGH percentage of esophageal malignancies proves to be inoperable upon exploration. The surgeon is then confronted with the onerous choice of allowing the patient to starve or of performing a gastrostomy or similar procedure.

This alternative presented itself a year ago during an exploratory laparotomy, in a case of epidermoid carcinoma of the esophagus with involvement of the aorta by direct extension. It was decided to attempt to establish a permanent artificial lumen through the malignant constriction by means of a rigid nonabsorbable tube. A silver tube was fashioned and inserted through a longitudinal slit in the lower end of the esophagus into its lumen. This tube, 9.4 cm. in length and 8 mm. in diameter, was then passed up through the constricting malignancy under direct vision. The passage of the tube was further facilitated by threading it upwards over a Levine tube. This prevented inadvertent perforation of the esophageal wall. The tube ends extended more than 3 cm. above and below the constriction. The tube had been slightly flanged

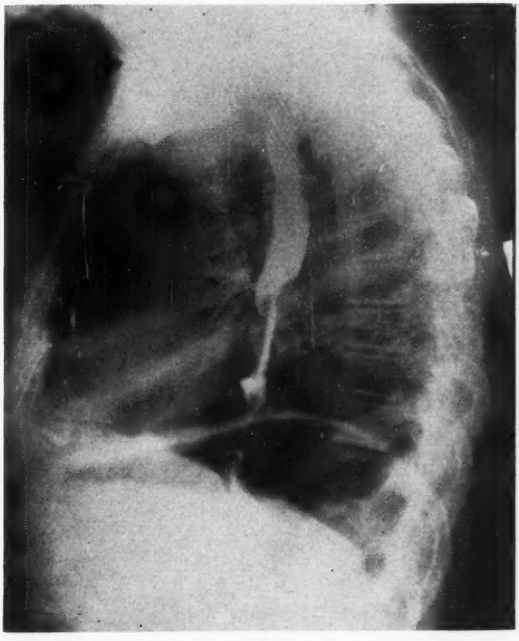
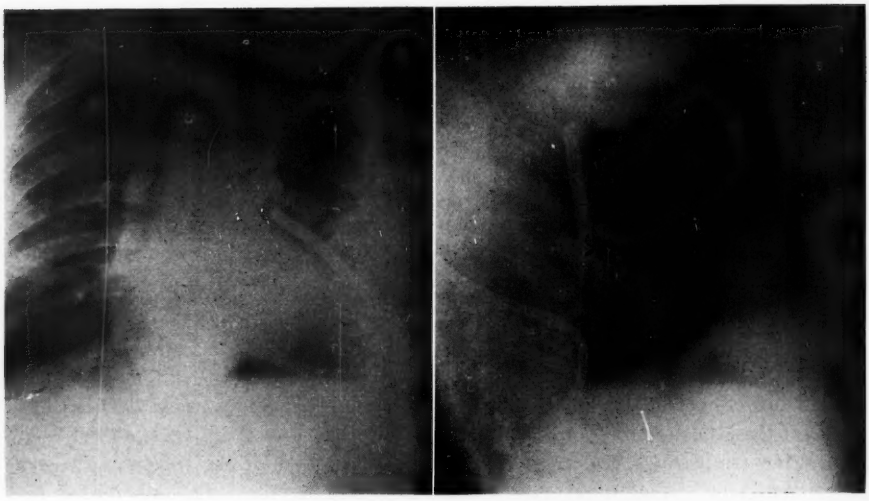


Fig. 1.—Lateral view of the esophagus showing irregularity of wall and site of constriction by tumor.

From the Department of Thoracic Surgery, Mount Zion Hospital.
Received for publication April 22, 1948.



A. *B.*

Fig. 2.—Anteroposterior and lateral views taken immediately after surgery showing position of metallic tube in midesophagus.

Fig. 3.—Appearance of esophagus six months after radiation and spontaneous passage of metal tube. The constriction noted above the diaphragm is, we feel, due to the cellophane ligature.

at its distal end. The attempt was then made to keep it in position by fixing the distal esophageal end in an "S" shaped manner to the posterior chest wall and by placing a flat ligature of cellophane around the esophagus just distal to the end of the tube, slightly constricting the esophagus at this point. These procedures formed a shelf which kept the tube from falling down toward the stomach and the flange kept it from passing upward into the buccal cavity.

It has been possible to feed the patient by mouth since operation. The diet is, of course, similar in consistency to that used through a gastrostomy tube but I do not believe that the manifold advantages of mouth feeding versus gastrostomy feeding need be stressed here.

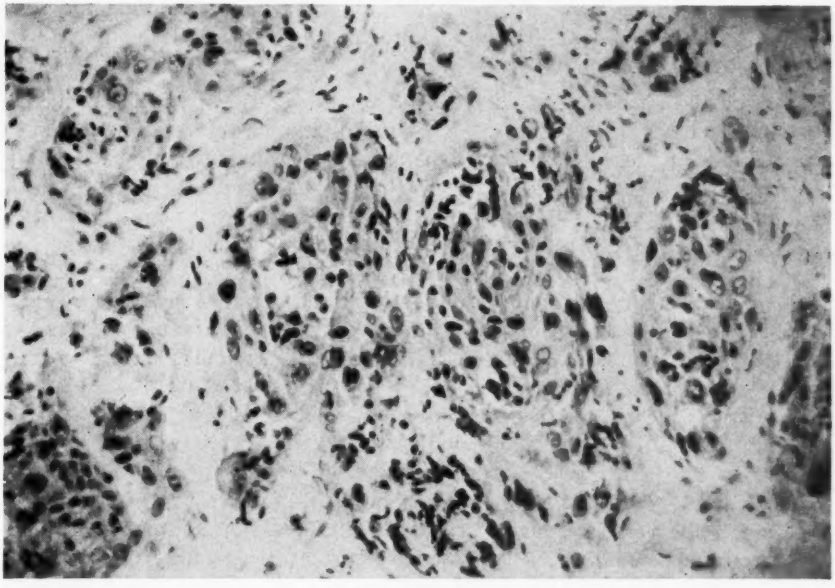


Fig. 4.—Microphotograph of the tumor tissue obtained preoperatively by biopsy done at esophagoscopy.

The patient was immediately treated by roentgen radiation according to the multiple-port method of Demy,* receiving a total of 20,000 r. over a period of thirty-one days, which gave an actual 5,000 r. to the tumor area. This caused a quick recession of the mass so that there was sufficient shrinkage to allow the spontaneous passage of the tube in thirty days. Esophagoscopy, six months after radiation, revealed a widely patent lumen throughout and no visible evidence of malignancy.

It is believed that whether or not a patient receives such benefit from radiation, the use of a rigid indwelling esophageal tube, as described above, may be worth while.

The exact material from which the tube should be fashioned to be most applicable for this purpose is at present under investigation.

*Demy, Nicholas G.: Beam Localization and Depth Dose Determination, Radiology 51: 89-99, 1948.

DECOLLATION OF INTRAPLEURAL ADHESIONS BY OPEN EXTRAPLEURAL PNEUMONOLYSIS

BRIAN C. THOMPSON, M.D.
DUNEDIN, NEW ZEALAND

ARTIFICIAL pneumothorax in the treatment of pulmonary tuberculosis is usually complicated by the presence of intrapleural adhesions. In many cases the lung can be effectively freed by thoracoscopy and internal pneumonolysis. Where adhesiotomy by this method cannot be achieved to a degree which allows adequate relaxation and cavity closure, modern authorities[5] advise that the pneumothorax be abandoned and alternative treatment, usually thoracoplasty, essayed.

While the physician may see little difference in magnitude between artificial pneumothorax and thoracoplasty, some, indeed, preferring the latter method without preliminary trial of the former, *(thoracoplastie d' emblée[6])* the patient is likely to hold different views. He sees a small operative mortality, not in broad actuarial terms, but with himself as possibly in the unlucky 5 per cent. Postthoracoplasty deformity, minimized though this may be by improved methods, is still a disagreeable prospect, especially to a young woman. This operation, in fact, is regarded by most patients as a last resort, to be accepted if there is no possible alternative.

We ought, therefore, before abandoning a pneumothorax because of indivisible adhesions, to consider carefully any other means by which it might be rendered effective. One method which has found limited favor is the so-called "fenestration" extrapleural pneumothorax.[7] This is performed in addition to the existing intrapleural pneumothorax, the two air spaces then being joined by cutting through the double pleural layer that divides them at that stage, the combined space being refilled thereafter as an ordinary intrapleural pneumothorax. This operation is not exacting to the patient and a hazard of earlier days, the introduction of secondary infection, is now mitigated by chemotherapy. However, an initially good result is very likely to become disappointing later. A good deal of blood inevitably oozes from the large raw area over the thoracic dome and even by early and frequent aspiration it is very difficult to keep the space dry. Whether for this reason, or because a broad flap of combined pleura is left hanging more or less free over the upper part of the relaxed lung, fresh adhesion tends to take place and is followed by firm organization between lung and chest wall. This occurrence, even if it does not immediately interfere with the collapse, is very often succeeded by loss of the space altogether by adhesive pleuritis.

By adopting a modification of this operation, we believe we have avoided these objections.

From the Tuberculosis Service, Otago Hospital Board, New Zealand.
Read at the Annual Meeting of the British Medical Association, New Zealand Branch, Feb. 4, 1948.
Received for publication May 11, 1948.

CASE REPORTS

CASE 1.—A salesman, aged 31 years, was found to have pulmonary tuberculosis in June, 1946, on routine examination after the death of his infant son from tuberculous meningitis. He had a cavitary lesion of moderate extent in the left upper lobe, with tubercle bacilli in the sputum. Left artificial pneumothorax was induced on August 8, and at successive thoracoscopies on October 11 and December 12 several fine apicoposterior adhesions were divided by galvanocautery. One short, broad, apicolateral adhesion was judged too dangerous to attempt, so that the lung was left firmly anchored to the chest wall at this point. The cavity remained patent, despite a crush of the left phrenic nerve to assist relaxation, and the sputum continued to contain tubercle bacilli (Fig. 1). At this juncture the patient was told that the pneumothorax must be abandoned and that he should prepare himself for thoracoplasty, a prospect for which he displayed no enthusiasm.

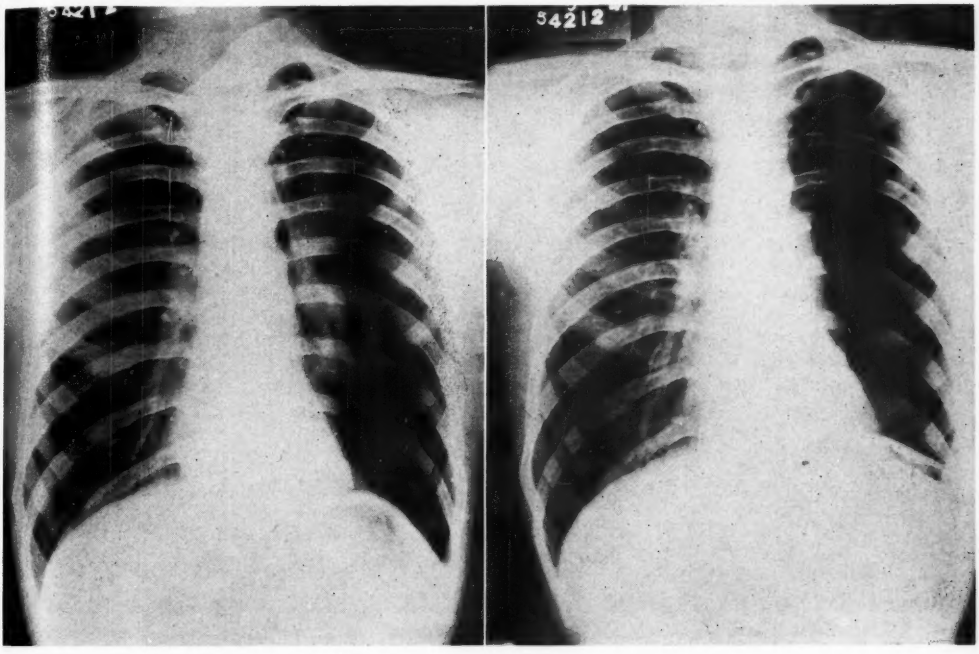


Fig. 1. Fig. 2.

Fig. 1 (Case 1).—With left artificial pneumothorax, after thoracoscopic division of adhesions and phrenic nerve crush. Lung still adherent, cavity patent.

Fig. 2 (Case 1).—After extrapleural decollation of the remaining adhesion. Lung completely free, cavity closed.

We decided, therefore, to compromise by attempting first a fenestration extrapleural operation, with the proviso that thoracoplasty might still ultimately be required. On Feb. 11, 1947, under basal narcosis and nitrous oxide inhalation, the chest was opened by removing a 4-inch section of the left fourth rib posteriorly. The periosteum was divided and parietal pleura was readily stripped from the endothoracic fascia by finger dissection over the apex of the lung. The circular base of the intrapleural adhesion, about 1½ inches in diameter, was now easily distinguished by palpation from the free pleural surface surrounding it. We knew from previous thoracoscopic examination that no other adhesion was present and we, therefore, decided to carry the stripping operation no further. A nick was made through the parietal pleura close to the base of the adhesion and was carried

around with scissors to a complete circle. The excised adhesion dropped back into the pleural cavity. The cut edges of the parietal pleura were sutured together and the wound closed in layers. Moderate subcutaneous emphysema developed during the next twelve hours but the patient had very little constitutional upset. An air refill of 500 c.c. was given on the second day and on the third day 600 c.c. of dark fluid blood were aspirated from the pleural cavity. Only 40 c.c. more were removed a day later, the usual difficulty being experienced in drying out the space. The remaining bloody exudate, however, became absorbed without any obvious adhesion taking place. The intrapulmonary cavity closed immediately, the sputum became negative for tuberculosis and soon disappeared (Fig. 2). The patient is today well and working, the pneumothorax being maintained by biweekly refills, with pressures on the negative side of zero.

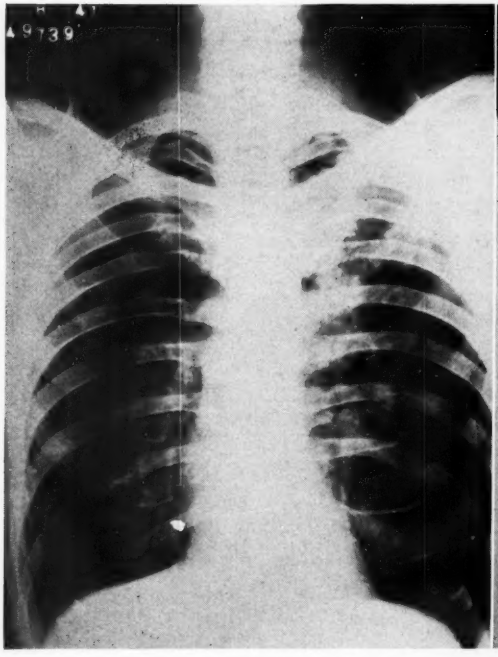


Fig. 3.

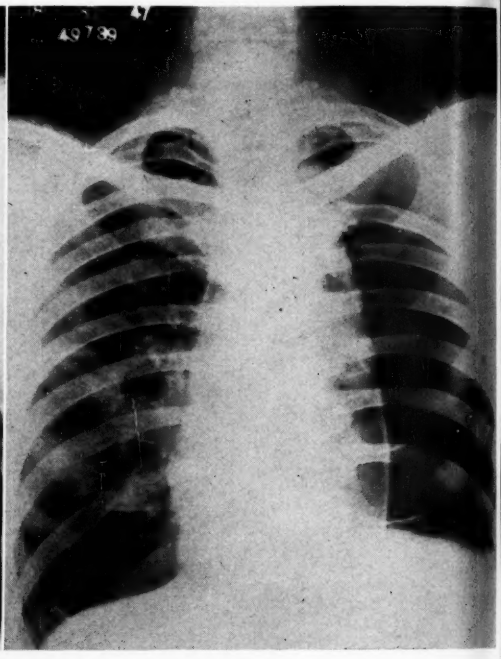


Fig. 4.

Fig. 3 (Case 2).—With left artificial pneumothorax. Lung adherent over a broad area, cavities still patent.

Fig. 4 (Case 2).—After decollation of the adhesion-complex. Lung collapsed against the mediastinum, cavities closed.

CASE 2.—This patient was a factory foreman, aged 44 years, with a tuberculous lesion detected in 1945. In June, 1947, definite activity was established, the lesion occupying the left lung apex with a cavity beneath the clavicle 1 inch in diameter. Artificial pneumothorax was induced on July 18. The roentgenologic appearances (Fig. 3) suggested that the lung was massively adherent over the apex and thoracoscopy was not attempted. On October 1 the chest was opened under local anesthesia, a 4-inch piece of the fourth rib being removed posteriorly, as in Case 1. The parietal pleura was stripped from the endothoracic fascia by blunt dissection until the whole vault was free. A fenestration was then made into the pleural cavity. Direct inspection revealed a number of stringlike adhesions which were easily divided by galvanocautery, leaving a broad apical symphysis. The pleural opening was carried right around this island of adhesion, which then dropped

back. The pleural edges were sutured and the wound closed. Apart from subcutaneous emphysema the patient experienced no postoperative effects and was transferred back to the sanatorium on the fifth day because he felt too well to be in a hospital ward. The lung was so far collapsed that no refill was necessary until October 28. Some effusion formed during this period but as it did not increase, no aspiration was performed until December 4, when 600 c.c. of clear, pale yellow fluid were removed. The pleural space has since remained dry and the lung cavity, which still appeared patent six weeks after operation, is now apparently closed (Fig. 4). The sputum is negative for tuberculosis and he has left the sanatorium, on biweekly refills of between 250 and 400 c.c.

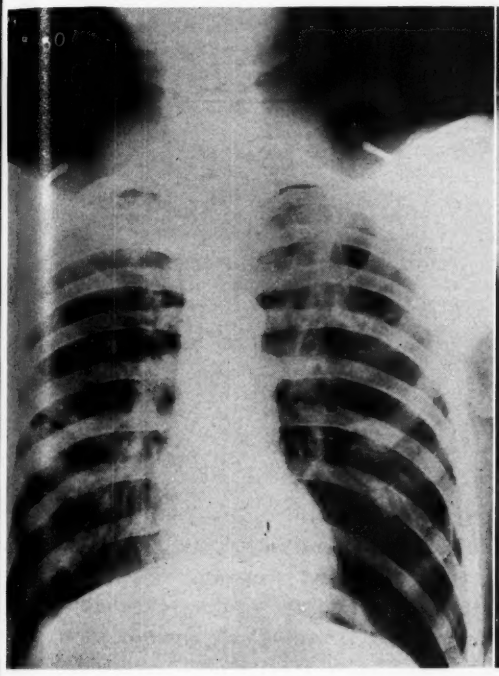


Fig. 5.

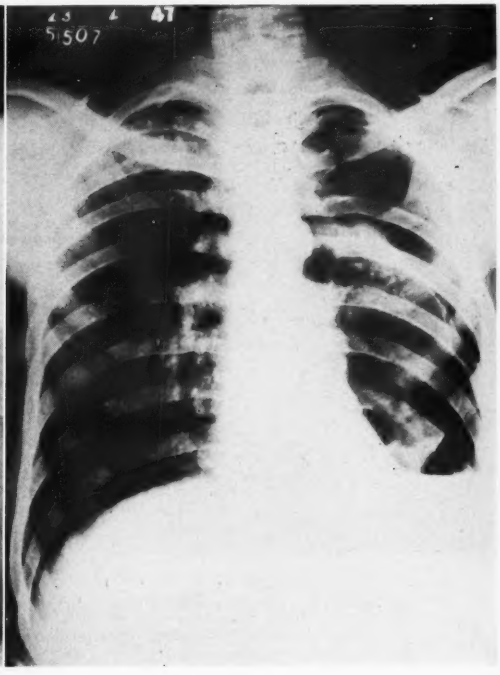


Fig. 6.

Fig. 5 (Case 3).—With left artificial pneumothorax. Lung widely adherent over the apex, cavity still patent.

Fig. 6 (Case 3).—After decollation of the adhesion. Lung completely free, cavity closed.

CASE 3.—A surgical-appliance technician, in a routine x-ray examination taken on discharge from the army in 1945, was found to have bilateral pulmonary tuberculosis. After six months of routine sanatorium treatment he was well enough to resume his civilian job, but signs of reactivation appeared in October, 1947, with a rise of the sedimentation rate to 20 mm. and the appearance of tubercle bacilli in the sputum. There was at this time infiltration in both lung apices with probable cavitation on the left. An artificial pneumothorax was induced on this side on October 22, but a massive adhesion was found to anchor the lung posterolaterally near the apex (Fig. 5). On December 2, under local anesthesia, a 3-inch piece of the fourth rib was removed posteriorly and the parietal pleura stripped as in previous cases over the thoracic vault. Opening up the pleural space showed a short symphysitic adhesion-complex which was enucleated by a circular section. The released lung fell back. The wound was closed in layers, the breach in the

parietal pleura being left unsutured. The postoperative course was uneventful, without even substantial subcutaneous emphysema. The patient returned to the sanatorium on the fourth day and had his first refill four days later. There was no significant intrapleural effusion. The pulmonary collapse is entirely satisfactory. (Fig. 6) and though there is still a trace of sputum this is negative for tuberculosis on culture.

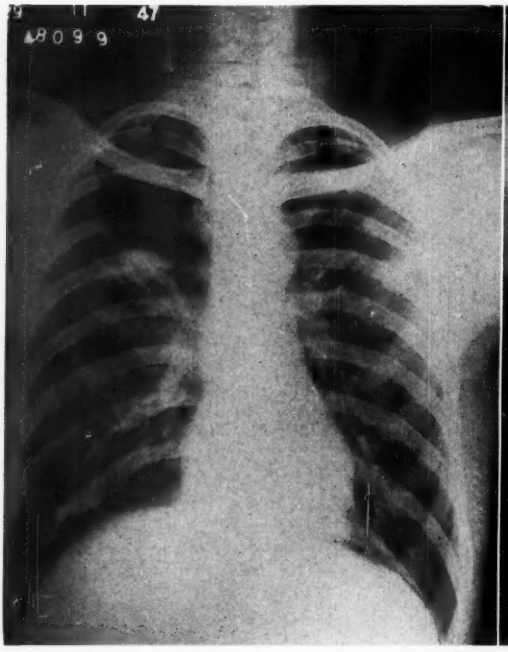


Fig. 7.

Fig. 8.

Fig. 7 (Case 4).—With right artificial pneumothorax, after thoracoscopic division of adhesions. Lung still anchored posterolaterally, cavity still patent.

Fig. 8 (Case 4).—After decollation of the remaining adhesion. Lung massively collapsed, cavity closed.

CASE 4.—A post-office clerk, aged 27 years was found to have pulmonary tuberculosis while on active service abroad in 1944. After rest treatment in various institutions, he returned to his job in the post office and kept well up to October, 1946, when he was admitted to hospital with hemoptysis. He came under our care in October, 1947, with extensive bilateral disease and tubercle bacilli in the sputum. A right artificial pneumothorax was induced on October 10, and on November 11, thoracoscopy was performed. Three apical strings were divided but a short, thick spool-shaped band running posterolaterally from the subapical part of the lung was judged too dangerous to interfere with intrapleurally. Fig. 7 shows the position after thoracoscopy. On December 1, a 3-inch section of the fourth rib was resected under local anesthesia. After separation of the parietal pleura, the base of the adhesion was found to lie directly beneath the exposed surface. Very little stripping was required to define its circular border, 1 inch in diameter, and an incision around this island base freed the lung completely. The wound was closed without suturing the parietal pleura. Next day the patient was rather dyspneic and was found to have a massive collapse of the right lung with displacement of the heart and mediastinum to the left (Fig. 8). No considerable effusion developed, however, and the lung gradually became aerated. The pneumothorax is now controlled by weekly refills of 500 c.c., the sputum is negative for tuberculosis and apparently the cavities are closed.

COMMENT

We have preferred an incision along the line of the fourth rib to the vertical paravertebral incision used by many surgeons for the operation of extrapleural pneumothorax.[1] This seems to give no greater tendency to subsequent limitation of movement if physiotherapeutic measures are instituted early. Active exercises are begun the day following operation. Penicillin, 15,000 units every three hours, is given parenterally as a routine for forty-eight hours after operation and then discontinued if the temperature is normal.

Preliminary thoracoscopy is an advantage, even if it seems likely that no adhesiotomy will be possible at that stage. In Cases 2 and 3 this was omitted, perhaps with no great loss. In Case 4, however, in addition to enabling us to free some adhesions, thoracoscopy showed us that the adhesion to be decollated extrapleurally was based right on the fourth rib, so that the usual posterior approach would lie directly over it. Thus, a very small area of stripping was required, with consequent absence of hemorrhage. We propose in the future always to approach the objective as closely as possible, unless, of course, more than one adhesion is involved.

DISCUSSION

We feel confident, even from a small experience, that we have evolved a method of liberating adhesions of a type that cannot be dealt with by internal pneumonolysis, because they are too short, or too massive, or too close to vulnerable structures, or too vascular, or because they contain lung tissue or tuberculous foci. If our technique has been used by others, we have found no published description, except of the extrapleural fenestration operation, of which it may be regarded as a development.

Adhesions in this class may sometimes be freed by *décollement* of their parietal attachments, either by means of the thoracoscope and cautery[3, 4] or by open thoracotomy[2] from within the pleural cavity. We are not persuaded that success can easily be achieved in this way except in the case of relatively small and mobile adhesions, where it is possible to define the limits of the basal island on every side. Even so, the subparietal area beneath remains an unknown factor. Local anesthesia from the intrapleural approach is difficult and the enucleation of the head of the adhesion is tedious and risky, even in experienced hands. Our technique, on the contrary, is exceedingly simple, free from risk of uncontrollable hemorrhage, and not much more exacting to the patient than a routine thoracoscopy. The area of operation is anesthetized, the adhesion base can be examined both intrapleurally and extrapleurally before detachment, there are no large vessels liable to damage. Tuberculous tissue is not likely to be opened unless the adhesive area is very dense, in which case no further pleural separation is attempted.

Our four cases make a modest total from which to draw conclusions. This is due to two factors. First, in the majority of patients with artificial pneumothorax where the treatment looks hopeful from the start, the lung can be effectively freed by thoracoscopic methods. Second, artificial pneumothorax

has in our practice been replaced in certain types of cases as it has come to be preceded in a great number of cases, by artificial pneumoperitoneum combined with, or without, phrenic nerve interruption. For this reason we have not yet found more instances in which extrapleural decollation appears indicated. We are encouraged to believe that its field may be widened, that a greater range of adhesions now regarded as indivisible and some difficult adhesions now attacked thoracoscopically with misgiving may instead be decollated extrapleurally and that timid patients may take courage in feeling that one further possibility exists for them between a failed thoracoscopy and the loss of their ribs.

SUMMARY

A technique is described for decollating intrapleural adhesions by open extrapleural pneumonolysis with the maintenance of an essentially intrapleural artificial pneumothorax.

Four cases are reported.

The thoracoscopic and extrapleural operations were performed in Dunedin Hospital by Mr. James A. Jenkins and Mr. Stanley L. Wilson, with both of whom the decollation technique was developed in close association.

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MEDIASTINAL TUMORS OF BLOOD VASCULAR ORIGIN

WILLIAM D. SEYBOLD, M.D.,* JOHN R. MCDONALD, M.D.†
O. THERON CLAGETT, M.D.,* AND STUART W. HARRINGTON, M.D.*
ROCHESTER, MINN.

THIS report deals with three surgical cases of mediastinal tumor in which the histologic picture was that of hemangioma or hemangio-endothelioma. These lesions were encountered among approximately two hundred mediastinal tumors treated surgically at the Mayo Clinic prior to Jan. 1, 1947. In addition, accounts of all mediastinal tumors of probable blood vascular origin in the available literature have been sought. Though no claim to completeness can be entered because of the extensiveness of the literature on mediastinal tumors in many languages and in many publications not generally available, a systematic and prolonged search yielded fourteen cases in which sufficient data were presented to make them acceptable as cases of probable blood vascular tumors of the mediastinum. The criteria for inclusion in this series were (1) location of the tumor in the mediastinum, (2) absence of a tumor in the lungs, (3) pathologic verification by post-mortem examination or by surgical exploration, and (4) the histologic picture of blood vascular spaces lined with endotheliomatous tumor cells. A conscientious effort has been made to avoid the error of including in this group highly vascular malignant tumors that were not of vascular origin.

Perhaps because of the protean nature of tumors in the mediastinum and even more because of the striking train of symptoms that results from progressively enlarging tumors in certain parts of the mediastinum, the literature abounds with reports of mediastinal tumors long before the introduction of the roentgen ray, which made reasonably early diagnosis possible, and, of course, long before the surgeon had successfully entered the chest for the removal of a tumor. In this early period, mediastinal tumors were generally considered to be malignant and were classified in two groups: carcinoma and sarcoma. The sarcomas were the more common, and they fall into the groups we recognize today as lymphoblastomas. The carcinomas were only slightly less common. They were usually thought to be primary in the mediastinum and frequently, as a terminal event, to invade the hila of the lungs. Many of these lesions described in detailed case reports of the last century we recognize today as primary bronchiogenic carcinomas which had invaded mediastinal nodes extensively and in which the secondary deposits of the tumor overshadowed the primary lesion. Occasionally, benign tumors were found and described. The dermoid cyst which today we classify as a dermoid type of teratoma received much attention and was occasionally recognized during life on the basis of the rather startling appearance of hair in the sputum.

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*Division of Surgery, Mayo Clinic.
†Section on Surgical Pathology, Mayo Clinic.

Our knowledge of the pathology of mediastinal tumors has advanced rapidly in the past twenty-five years following closely in the wake of new knowledge of respiratory physiology that has enabled the anesthetist to control respiration in the presence of an open pneumothorax and the surgeon to attack boldly and confidently an ever-increasing variety of lesions in the chest.

The ability of the surgeon to remove, with reasonable safety, circumscribed lesions within the mediastinum has made accurate knowledge of the variety and of the natural history of these lesions essential for an intelligent approach to the problem presented by a patient with an intrathoracic tumor.

Roentgen-ray examination of large numbers of apparently healthy persons has disclosed many mediastinal and other intrathoracic lesions which went undiagnosed in the past because symptoms are uncommon in the early life of these tumors. Successful surgical removal of many such lesions has permitted valuable pathologic and clinicopathologic studies, but since our knowledge of these tumors is still young and incomplete, reports of unusual and rare lesions make worth-while contributions to our rapidly accumulating knowledge in this field.

A number of excellent reviews of the subject of mediastinal tumors in general have been published recently[1, 2] and the experience of thoracic surgeons in the armed forces of the United States in World War II has been responsible for a number of interesting reports[3, 4, 5] concerning the incidence of mediastinal tumors in large numbers of young men and women undergoing roentgen examination of the chest and concerning the relative incidence of the several pathologic varieties. In the monograph of Heuer and Andrus[1] mediastinal tumors of blood vascular origin were not mentioned. In one hundred and nine mediastinal tumors removed surgically and reported on by Blades[3] there was no example of a tumor of blood vascular origin, and in thirty-three cases reported on by Watson and Diamond[4] there was a single instance of hemangioma of the mediastinum (Table I).

In 1944 Adams and Bloch[6] reported a case of hemangioma of the mediastinum (Table I). They were able to find but one previously recorded case (Winkelbauer's[7]) in the literature. Our own extended search uncovered a few more cases which we think should properly fall in this group, but at the same time it served to reemphasize the rarity of these lesions.

Among approximately two hundred mediastinal tumors that were removed surgically at the Mayo Clinic prior to Jan. 1, 1947, there were three which seem to satisfy the criteria we previously set forth for a mediastinal tumor of vascular origin. In Table I we have summarized the reports on the fourteen cases we have been able to collect from the literature and the data on the three cases of our own. Brief accounts of each of the latter three follow. The case numbers correspond to those in Table I.

TABLE I. SUMMARY OF REPORTS OF CASES OF MEDIASTINAL TUMORS OF BLOOD VASCULAR ORIGIN

					EVIDENCE OF MALIGNANCY	

REPORT OF CASES

CASE 15.—A 27-year-old man registered at the clinic on Sept. 15, 1941, complaining of a feeling of pressure in the chest of three weeks' duration. According to his account he had been in good health until eight months before, when he began to lose weight. Four months later he had chills, fever, and generalized pains. During the two weeks these acute symptoms

TABLE I. SUMMARY OF REPORTS OF CASES OF MEDIASTINAL TUMORS OF BLOOD VASCULAR ORIGIN

CASE	AUTHOR; YEAR	SEX	AGE, YEARS	PATHOLOGIC DIAGNOSIS	EVIDENCE OF MALIGNANCY			OUTCOME	PHOTOMICROGRAPH
					HISTOLOGIC	INVASIVENESS	METASTASIS		
1	Heuer,[13] 1924	M	33	Endothelioma (needle biopsy)	Yes	Yes	?	Died 4 months after operation	No
2	Heuer,[13] 1924	F	17	Pleural endothelioma	Yes	No	No	Living and well, 2 years	Yes
3	Hosoi and Stewart,[14] 1931	F	61	Malignant endothelioma	Yes	No	No (autopsy)	Died 27th hospital day	Yes
4	Lilienthal,[15, 16] 1927	F	4	Angiosarcoma? Hemangiosarcoma	Yes	Capsule posteriorly	No	Living and well, 10 years. Tumor disappeared on roentgenogram	Yes
5	Bencini,[17] 1936	—	18 days	Angioma	?	?	?	Died aged 18 days. Referred to by Bergstrom	No
6	Döderlein,[18] 1938-39	—	Premature infant	Hemangioma	?	?	?	Referred to by Bergstrom. Death in a few days	No
7	Bergstrom,[19] 1945	F	3.5 weeks	Hemangioma	No	Yes	No	Death in 4 weeks	Yes
8	Bergstrom,[19] 1945	F	5 weeks	Hemangioma	No	Yes	No	Death in 2 days	Yes
9	Adams and Bloch,[6] 1944	M	34	Hemangioma	No	Yes	No	Living and well, 4 years. Incomplete surgical removal	Yes
10	Winkelbauer,[7] 1929	M	29	Malignant hemangio-endothelioma	No	No	Yes	Died 2 months after operation. Local recurrence and metastasis	No
11	Kott,[20] 1922	F	36	Angiosarcoma	Yes	Yes	Yes	Died 7 months after first visit	No Postmortem histopathologic description
12	Stewart,[21] 1888	M	32	Angiosarcoma	Yes	Yes	Yes	Died 8 months after onset	Yes Complete postmortem description
13	Watson and Diamond,[4] 1947	—	—	Hemangioma	—	—	—	Not given	No
14	Shennan,[12] 1914	F	23	Angioma	No	Yes	Yes	Died	Yes
15	Authors, 1948	M	27	Hemangio-endothelioma	Yes	Yes	Yes?	Died 2 months after exploration	Yes
16	Authors, 1948	M	18	Hemangio-endothelioma	Yes	Yes	No	Living and well 3.5 years after operation	Yes
17	Authors, 1948	M	59	Hemangioma	No	No	No	Living and well 14 months after operation	Yes

were present, he was irrational part of the time. A roentgenogram of the chest revealed a tumor which was said to displace the trachea and the heart. For this he was given a course of deep roentgen-ray therapy which, according to his story, was followed by some regression in the mass. Three weeks prior to his registration at the clinic, a sensation of pressure in the chest, a cough productive of thick, mucoid sputum, night sweats, dyspnea on exertion, and anorexia had developed. He had lost thirty pounds (13.6 kilograms) since the onset of his illness.

The past history and family history were not significant.

On physical examination he was found to be thin and pale. The blood pressure was 124 systolic and 68 diastolic, expressed in millimeters of mercury. The pulse rate was 112 per minute and the oral temperature 99.3° F. During the course of the examination there were frequent paroxysms of coughing. Examination of the chest revealed signs of consolidation in the left side with shift of the heart and mediastinum to the right.

A roentgenogram of the chest showed a circumscribed shadow lying anterior to the left pulmonary hilum between the second and fourth ribs (Fig. 1, *a* and *b*). Roentgenoscopic examination yielded the additional information that the mass did not have an expansile pulsation. Our films were compared with those that had been made by the patient's physician at home and some increase in the size of the tumor was apparent.

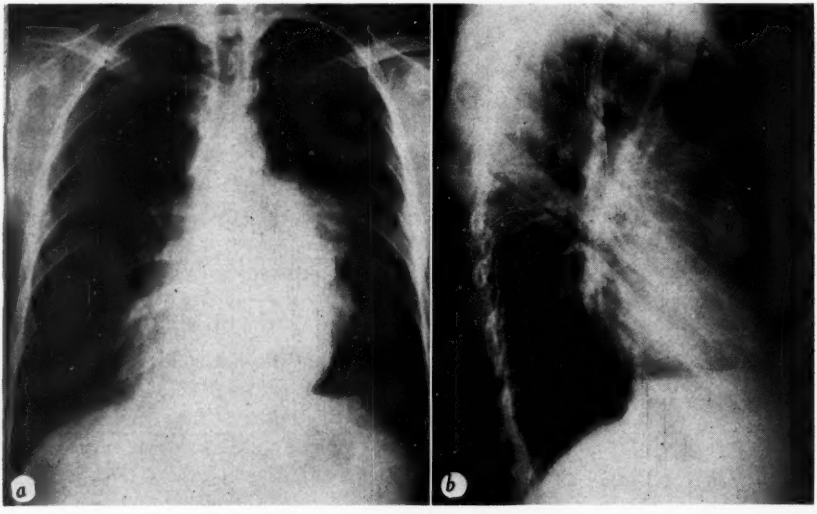

Fig. 1 (Case 15).—*a*, Posteroanterior view. *b*, Left lateral projection showing the anterior position of the mass.

Routine laboratory studies revealed normal urine, a moderate anemia, a normal leucocyte count, and a negative serum flocculation for syphilis.

Exploratory thoracotomy was advised and on Sept. 26, 1941, the left side of the chest was explored, an anterior approach being used. A huge, obviously malignant tumor practically filled the entire mediastinum, compressing the left lung laterally and pushing the heart to the right. The tumor was invading the pericardium and structures in the anterior mediastinum, and it could not be removed. Biopsy revealed hemangio-endothelioma, grade 1 (Broders) (on a basis of 1 to 4, in which 1 represents the least and 4 the most malignant condition) (Fig. 2).

Postoperatively, the patient failed rather rapidly. There were signs of progressive superior vena caval obstruction, pain was severe, and death came on Dec. 1, 1941, after his

return home. Post-mortem examination was not done, but an account of the manner of his death in a letter from his wife suggested that cerebral metastasis probably had developed as a terminal event.

Microscopic Description.—Histologically, the lesion had the appearance of a capillary hemangio-endothelioma (Fig. 2, *a* and *b*). Most of the spaces were empty, but a few were filled with blood. These spaces were lined with round cells. In some areas sheets of endothelial cells replaced the vascular spaces. There was moderate pleomorphism. Mitotic figures were scarce. There were areas of necrosis and fibrosis, and a number of deposits of hemosiderin. The pathologic diagnosis was hemangio-endothelioma, grade 1.

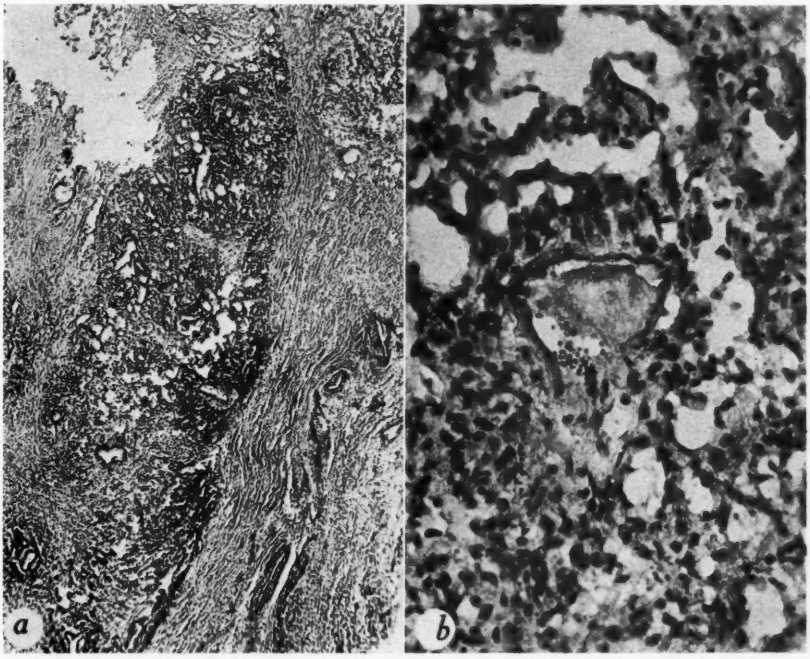

Fig. 2 (Case 15).—*a*, Section of biopsy specimen (hematoxylin and eosin ×26). *b*, Same section as in *a*, showing vascular spaces and large endotheliomatous cells (hematoxylin and eosin ×200).

CASE 16.—An 18-year-old boy registered on March 31, 1944, because of a tumor in the right side of the chest which had been found on roentgen-ray examination at an army induction center in October, 1943. Since the age of 9 or 10 years he had occasionally experienced a dull, aching pain in the region of the third and fourth lumbar vertebrae. During the previous two years this pain had become more severe, and in addition, he had experienced recurrent, severe, sharp pain beginning in the right upper abdominal quadrant under the costal arch and extending across the abdomen. During these two years he had lost ten pounds (4.5 kilograms), but his general health had been good.

The family history and the past history were not significant.

The physical examination gave essentially negative results. The blood pressure in the brachial artery was 120 systolic and 70 diastolic. The pulse rate was 68 per minute and the temperature 98.4° F. Physical and roentgenologic examinations of the spinal column resulted in a diagnosis of spondylolisthesis. The pain in the back was ascribed to this defect.

A roentgenogram of the chest showed a rounded mass approximately 2.5 inches (6.4 cm.) in diameter in the right posterior part of the chest adjacent to the spinal column at the level of the ninth and tenth thoracic vertebrae (Fig. 3, *a* and *b*). There was some erosion of the tenth rib. Roentgenograms made in October, 1943, were available for comparison; no real change was apparent. A tentative diagnosis of mediastinal neurofibroma was made and thoracotomy was advised.

On April 19, 1944, right thoracotomy was done through a posterolateral incision along the ninth rib, the greater part of which was excised subperiosteally. There was a large, well-circumscribed tumor lying in the posterior costovertebral sulcus extending from the upper edge of the ninth rib at its attachment to the vertebral body to a level slightly below the eleventh rib. The tumor was external to the pleura and there were many large, tortuous vessels, both arteries and veins, lying on its surface. The tumor was visibly and palpably expansile. When the pleura overlying it was incised and mobilization of the lesion was begun, bleeding was profuse and difficult to control. The tumor itself was quite friable and vascular. Hemostasis was accomplished by controlling all vessels, including the underlying intercostal vessels at the circumference of the tumor. There was no gross evidence of invasion of structures in the intercostal spaces or of the ribs. The bed of the tumor was covered with pleura. The lung was inflated, and the thoracic wall was closed. The patient received 1,750 c.c. of whole blood during the course of the procedure.

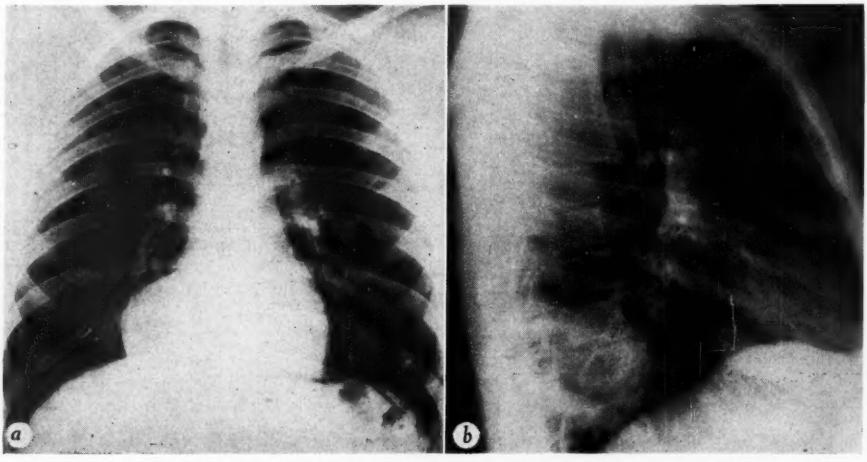

Fig. 3 (Case 16).—*a*, Posteroanterior view. *b*, Right lateral projection showing the posterior position of the mass and absence of enlargement of the intervertebral foramen as is sometimes seen in neurogenic tumors in the posterior mediastinum.

After the operation the patient made a rapid and uncomplicated recovery. He was dismissed from the hospital on his twenty-first postoperative day. Because of the histologic character of the tumor, roentgen-ray therapy was given postoperatively.

Pathologic Description.—The tumor was oval and measured 5 by 4 by 7 cm. In cut section it was quite vascular, and there were numerous areas of hemorrhage and necrosis. It was well circumscribed, and its capsule was complete except at the site of rather broad attachment to the thoracic wall (Fig. 4).

Multiple blocks from widely separated parts were taken for microscopic study. Histologically, the tissue had a capillary and cavernous pattern (Fig. 5, *a* and *b*), and in some areas the vascular spaces were replaced by sheets and columns of endothelial cells. Most of these cells were round, but some were inclined to be spindle-shaped and to line spaces, some

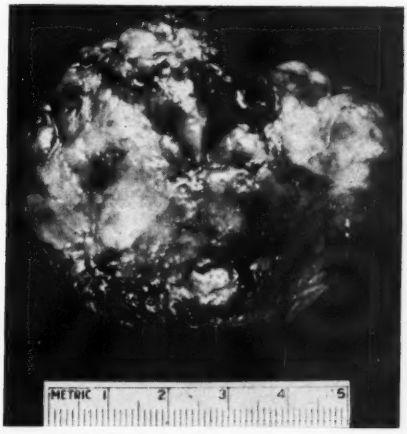

Fig. 4 (Case 16).—Surgical specimen.

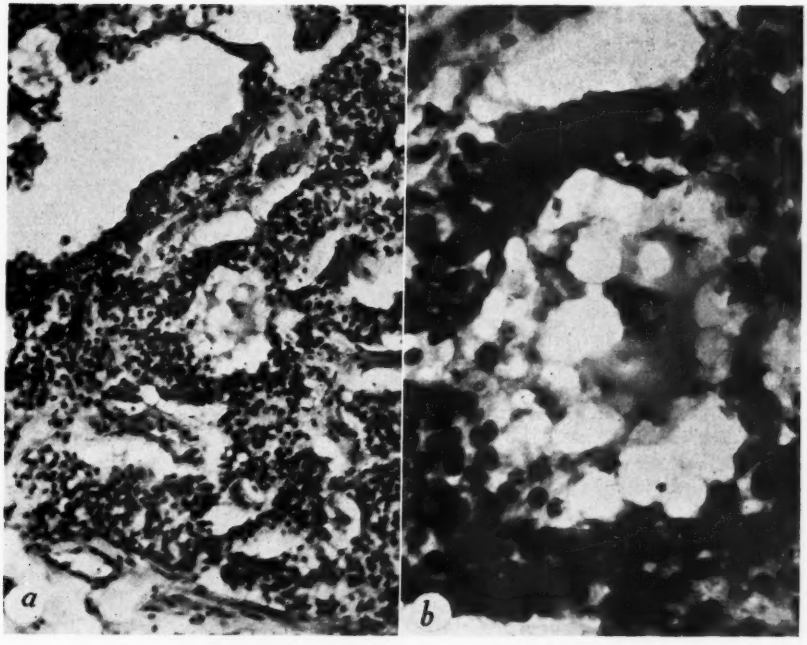

Fig. 5 (Case 16).—*a*, Demonstration of capillary and cavernous vascular pattern (hematoxylin and eosin ×125). *b*, Same section as in *a* (Hematoxylin and eosin ×435).

of which contained blood; mitotic figures were scarce and nucleoli were not prominent. Hyperchromatism and irregularity in size of the nuclei existed in moderate degree. There were numerous fibrous trabeculae throughout the tumor.

In one place, invasion of a thoracic sympathetic ganglion by the tumor was apparent (Fig. 6, *a* and *b*).

In a letter dated April, 1947, the patient reported that he had been in good health since his dismissal here three and one-half years previously.

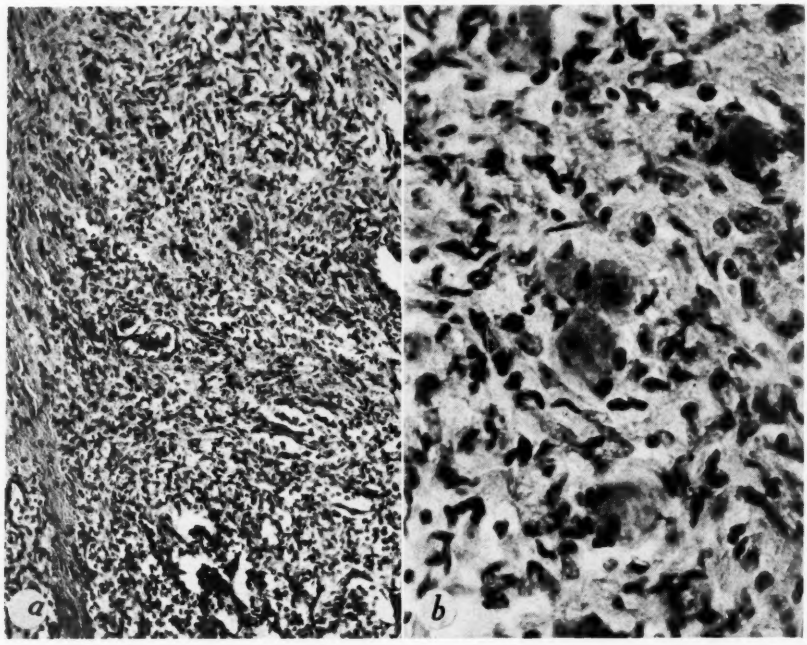

Fig. 6 (Case 16).—Sympathetic ganglion cells surrounded by tumor tissue. Stained with hematoxylin and eosin. *a*, ×90. *b*, ×365.

CASE 17.—A 59-year-old man registered at the clinic on Sept. 19, 1946, because of a tumor in the chest that had been discovered on roentgen-ray examination during the course of a routine clinical examination five months before. There had been no change in his general health and no local symptoms. The family history and past history were not significant.

On physical examination he was found to weigh 150 pounds (68 kg.). The blood pressure in the arms was 130 systolic and 88 diastolic; the pulse rate was 80 per minute and the temperature 99° F. He was well developed and well nourished. The only abnormal findings were bilateral inguinal herniae and varicosities of the saphenous veins.

Roentgenograms of the chest revealed a rounded, well-circumscribed mass approximately 3 cm. in diameter which appeared to be in the superior division of the right lower lobe (Fig. 7, *a* and *b*). There were several small calcified hilar lymph nodes in the left lung. Roentgenograms of the thoracic part of the spinal column showed minimal hypertrophic arthritic changes.

Urinalysis and routine examination of the blood, including determination of hemoglobin and erythrocyte and leucocyte counts, did not yield any abnormal data. The serum flocculation test for syphilis gave negative results.

A clinical diagnosis of intrathoracic neurofibroma was made and thoracotomy was advised.

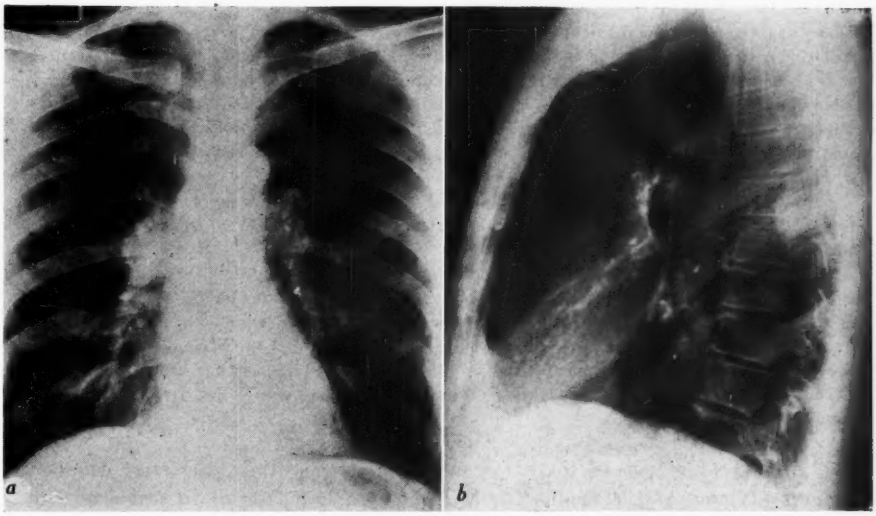

Fig. 7 (Case 17).—*a*, Posteroanterior view showing the mass in the region of the right pulmonary hilum. *b*, Right lateral projection showing the posterior position of the tumor.

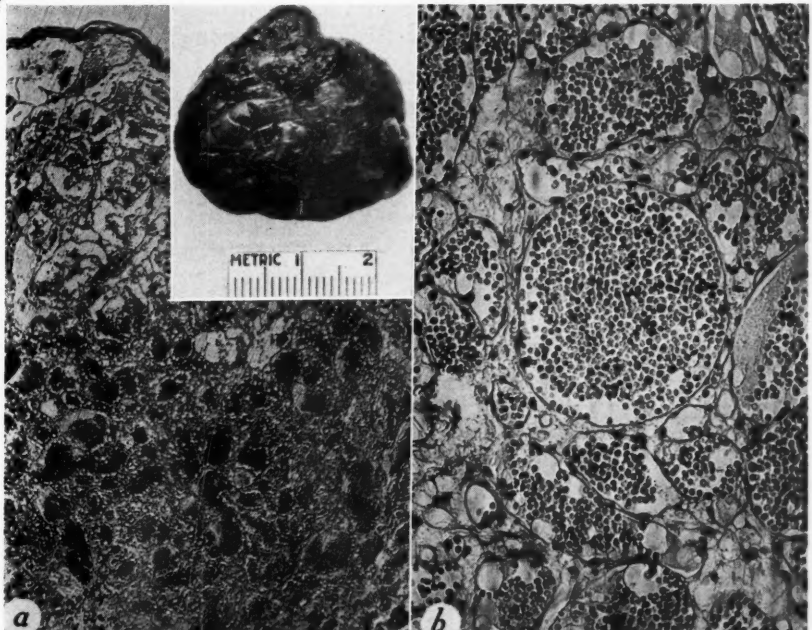

Fig. 8 (Case 17).—*a*, Capillary and cavernous hemangioma (hematoxylin and eosin ×25). *b*, Same section as in *a* (hematoxylin and eosin ×200). *Inset*, Well-encapsulated hemangioma.

On Oct. 19, 1946, the right chest cavity was explored through the bed of the seventh rib. There was a soft, purple, obviously vascular tumor arising in the region of the seventh interspace posteriorly, about 1.5 inches (3.8 cm.) from the spinal column. It was extrapleural and well encapsulated, and it was removed in toto without difficulty. Some oozing of blood from the bed of the tumor was controlled with mattress sutures. The intercostal vessels in the corresponding interspace did not appear dilated after the tumor was enucleated, the defect in the pleura was closed, the lung was inflated, and the thoracic wall was closed in layers without drainage.

The cut surface of the tumor was dark red and spongy in appearance. No large vessels could be identified in the pedicle. The tumor measured 3.5 by 3.7 by 2.5 cm. and weighed 12 Gm. (Fig. 8, *inset*).

Microscopic Anatomy.—There were many capillary and cavernous spaces, most of which were filled with blood (Fig. 8, *a* and *b*). In some of these spaces endothelial cells seemed to be piled up two and three deep, but in most they formed a single layer. The endothelial cells tended to be spindle shaped. No mitotic figures were found, and the hemangiomatous tissue was intersected by a few fibrous trabeculae. The pathologic diagnosis was hemangioma.

In a letter dated Dec. 5, 1947, the patient stated that he was well and free of symptoms.

COMMENT

In the experience of the surgeons at the Mayo Clinic, the most common primary tumors of the mediastinum are benign lesions, and in order of frequency they are tumors of nerve origin (neurofibroma, ganglioneuroma), teratoid tumors, and mediastinal cysts. Uhrich[8] studied 160 primary mediastinal tumors removed surgically at the clinic prior to Jan. 1, 1945. The pathologic classification and relative incidence are shown in Table II. These figures agree rather closely with those published by Blades,[3] Watson and Diamond,[4] and others.[1, 2, 5]

TABLE II. PRIMARY MEDIASTINAL TUMORS TREATED SURGICALLY (UHRICH)

BENIGN		MALIGNANT	
TYPE OF LESION	CASES	TYPE OF LESION	CASES
Primary nerve tumor	53	Thymoma	17
Teratoid tumor	29	Miscellaneous	7
Mediastinal cyst	18	Chondrosarcoma	6
Fibroma	5	Hemangio-endothelioma	4*
Chondromatous tumor	5	Teratoid tumor	4
Thyroid adenoma	3	Bronchiogenic cyst	1
Lipoma	2	Neurofibrosarcoma	1
Myxoma	1	Fibrosarcoma in a fibroma	1
Hamartoma	1	Liposarcoma	1
Parathyroid adenoma	1		
Total	118	Total	42

*Two of these cases are included in the present report (Cases 15 and 16). The data in the other two cases were reviewed by us and the lesions were reclassified as extremely vascular undifferentiated malignant tumors.

By all accounts, tumors of blood vascular origin in the mediastinum are rare. Though benign hemangiomas occur rather commonly in the skin and in many of the abdominal organs, hemangio-endotheliomas are rather uncommon in all situations. Furthermore, the tumors that have been classified as hemangio-endothelioma and endothelioma form a heterogeneous and controversial group. There are a number of factors which make classification difficult. As Ewing[9] has stated, "the demands for nutrition in rapidly growing cellular tumors may produce a type of growth which is composed chiefly of blood vessels sheathed

by masses of tumor cells, and which is often called perithelioma, or telangiectatic sarcoma. This rather characteristic structure is not confined to any one class of tumors and it is not essentially a tumor of blood vessels." He defines true angiomas as "a larger class of tumors in which a neoplastic process affects the walls of vessels and usually also the supporting connective tissue." Ewing's concept of endothelioma is also that which has been widely held, and his definition and discussions describe lucidly the complexity of the group and the controversial issues. "The term endothelioma is applied to an extensive group of tumors which are believed to be derived from the living cells of blood vessels, lymph vessels and spaces, subdural spaces, and serous cavities.

"The scope of endotheliomas has suffered wide fluctuations because of the uncertainty surrounding the embryonal relations of different classes of endothelial cells, the peculiar position occupied by these cells as intermediate between epithelium and fibroblasts, and the difficulty of determining the origin of many tumors supposed to belong to this class. Thus some authors find the group extremely numerous and complex, while others, insisting upon more rigid data, describe a restricted class of tumors as endothelioma." This quotation has been taken from Ewing in order that we may clearly and unmistakably present the concept we have accepted and tried to adhere to in presenting the reports of our three cases and in searching the literature for others. According to our concept, endotheliomas comprise a very limited group, and hemangio-endotheliomas comprise, of course, an even more narrow and less numerous one. We have tried to limit ourselves to those tumors in which the evidence supported a blood vascular origin. Our definition agrees closely with that of Bell[10] who defined hemangio-endothelioma as a form of angioma comprised of blood vessels in early stages of formation. Blood does not necessarily circulate through the vessels of the tumor since they are incompletely differentiated. In incompletely differentiated parts of the tumor the endothelial cells form sheets or cords. In other parts of the tumor, numerous endothelial-lined spaces are present and blood is commonly found in a number of them. Histologic evidence of malignancy is judged on the basis of lack of cell differentiation, the number of mitotic figures, and the invasion of contiguous tissues.

The diagnosis of a simple cavernous and capillary hemangioma offers little room for error or for controversy.

Malignant tumors of blood vascular origin which metastasize to other parts of the body are very rare. Benign hemangiomas, on the other hand, are rather common. They may be localized and well circumscribed, or they may grow slowly and invade contiguous tissues.[11] The majority of multiple hemangiomas are multiple primary growths and not metastatic tumors, since the individual tumors are histologically benign[10]; however, histologically benign, metastasizing angiomas perhaps do occur.[12]

In our two cases in which the diagnosis of hemangio-endothelioma was made there was histologic evidence of malignancy and there were gross evidences of invasiveness in one instance and microscopic evidence of invasive-

ness in the other. One of these patients who had a lesion which was locally inoperable died a few months later apparently as a result of the neoplasm. The second patient survived more than three years without evidence of recurrence or distant metastasis. Our third patient had a neoplasm that grossly and microscopically was benign. He survived operation and was in good health when last seen more than a year after operation.

Symptoms and Signs.—The clinical picture presented in each of the seventeen cases (Table I) varied widely and was dependent as it always is in mediastinal tumors, on the size and the position of the growth. Symptomatically, there was nothing unique or unusual in the majority of cases. There were at least two exceptions to this statement, however. The patient reported by Lilienthal[15, 16] (Case 4, Table I) had a very unusual story, but rare cases of disappearance of a malignant lesion and long survival of the patient have been reported in carcinoma of the stomach, colon, breast, and other organs. The other exception was the presence of a palpable pulsation or an audible bruit over the tumor in three cases. These signs, of course, are not pathognomonic, for they are more common in the presence of an aneurysm or an arteriovenous fistula. Pain was usually the result of malignant invasive lesions. Respiratory embarrassment followed involvement of the pericardium or diaphragm, or the displacement of a large volume of pulmonary tissue. At least three of the lesions were discovered on routine roentgen-ray examination of the chest. As with any mediastinal tumor, cough, and hoarseness may be present, and they may signify involvement of the tracheobronchial tree and the left recurrent laryngeal nerve, respectively.

All subdivisions of the mediastinum were involved with apparently equal frequency.

Sex and Age.—In the seventeen cases available for analysis in this review, there was equal sex distribution, and the lesion was predominantly one of young individuals. Fourteen of the seventeen patients were less than 41 years of age, and four were under 1 year (Table III).

TABLE III. SEX AND AGE OF 17 PATIENTS WITH MEDIASTINAL TUMORS OF BLOOD VASCULAR ORIGIN

SEX	CASES
Male	7
Female	7
Not stated	3
Total	17
AGE, YEARS	
Under 1	4
1-10	1
11-20	2
21-30	3
31-40	4
41-50	0
51-60	1
61-70	1
Not stated	1
Total	17

Extremes of age: premature infant to 61-year-old woman.

Behavior of the Tumors.—In eight of the seventeen cases, there was histologic evidence of malignancy. In six there was histologic evidence of benignancy and in three the available information was insufficient to permit independent interpretation. One of the lesions we are including in the benign group was reported simply as an hemangioma.[4] Definite evidence of distant metastasis existed in five cases, in two of which the primary lesion had the appearance of benignancy. In Table IV, these data together with simple figures on operability are summarized. In the attempt to evaluate the data on operability, it must be understood that the patients under consideration included infants and stillborn infants, along with several patients who succumbed to their lesions long before the contents of the thoracic cage were considered to be in the domain of the surgeon. These figures on operability, then, mean little and cannot be applied to clinical practice today.

TABLE IV. PATHOLOGIC CHARACTER OF MEDIASTINAL TUMORS OF BLOOD VASCULAR ORIGIN IN 17 CASES

CHARACTER OF TUMOR	PATIENTS		
	TOTAL	TREATED SURGICALLY	LIVING
Histologically malignant	8*	3	2
Evidence of metastasis	3		
Histologically benign	6	4†	2
Evidence of metastasis	2		
Histologically indeterminate on basis of available data	3		

PATHOLOGIC DIAGNOSIS IN ORIGINAL REPORTS

DIAGNOSIS	CASES
Endothelioma	1
Pleural endothelioma	1
Malignant endothelioma	1
Hemangiosarcoma	1
Angioma	2
Hemangioma	6
Malignant hemangio-endothelioma	3
Angiosarcoma	2

*Lilienthal's patient (Case 4, Table I) was living and well ten years after his original report. She had received no surgical treatment.

†In Case 13 no follow-up has been reported.

A brief statement as to the outcome in each of the six patients in whom surgical removal of the lesion was accomplished is given in Table V. Four of the six patients were alive and well at the time of the last available report. Two of these four had lesions which were histologically malignant. One was followed up twenty-four months and the other forty-two months. A third member of this group had a lesion which could not be removed completely because it had invaded the pericardium, though the histologic picture was that of benignancy. This patient was alive and well four years later, at the time of Adams and Bloch's report in 1944. Though the prognosis must remain guarded in these patients, the lesions commonly are of a low order of malignancy, and equally commonly, they are benign.

TABLE V. OUTCOME IN 6 CASES IN WHICH THE LESION WAS REMOVED SURGICALLY

CASE	OUTCOME
2	Patient living and well at last report two years postoperatively. Tumor was histologically malignant.
9	Patient living and well four years postoperatively. Tumor was invasive grossly but histologically benign.
10	Patient died two months postoperatively of local recurrence and metastasis.
13	No follow-up reported. Lesion was called benign hemangioma.
16	Patient living and well 42 months postoperatively. A recent roentgenogram of the chest failed to reveal evidence of local recurrence or pulmonary metastasis. Histologically, the lesion was malignant and had invaded a dorsal sympathetic ganglion.
17	Patient living and well 14 months postoperatively. Lesion was benign histologically and was called an hemangioma.

SUMMARY AND CONCLUSIONS

This report has dealt with three cases of mediastinal tumor in which the histologic picture was that of hemangioma or malignant hemangio-endothelioma; these three tumors were encountered among approximately 200 mediastinal tumors treated surgically at the Mayo Clinic prior to Jan. 1, 1947. A careful, though necessarily incomplete, perusal of the literature on mediastinal tumors brought to light reports of fourteen additional cases of blood vascular origin.

A studious attempt has been made to avoid the easy error of including any highly vascular malignant neoplasm in this group. Only those cases have been included in which the evidence for blood vascular origin of the tumor seemed reasonably complete.

Primary mediastinal tumors are uncommon; those of blood vascular origin are rare. The most frequent lesions among them are benign tumors of nerve origin and cystic lesions of teratomatous or enterogenous origin. Many other varieties have been reported.

In two of our three cases there was evidence of malignancy. One patient had a lesion that had invaded surrounding mediastinal structures and that was too extensive for surgical removal; the other had a lesion which was histologically of low-grade malignancy and which had invaded a contiguous sympathetic ganglion. The third patient had a benign hemangioma.

Of the fourteen cases gleaned from the literature there was evidence of malignancy in eight. In six of these the lesions were histologically malignant, and in two the lesions were called histologically benign but there were regional and distant metastases.

Of the entire group of seventeen patients, surgical removal of the lesion was accomplished in six; four of these six were living at the time of the last available reports. This cannot be interpreted in terms of operability for some of these patients came under observation long before lesions in the mediastinum were surgically accessible.

There is evidence to support the contention that so-called benign hemangiomas associated with metastatic tumors are in reality multiple primary le-

sions. The outlook for a patient with a single, well-encapsulated, histologically benign hemangioma of the mediastinum is probably excellent. Even when it is not well encapsulated and cannot be completely removed, the outcome is hopeful on the basis of the report of Adams and Bloch whose patient was alive and well four years after operation. The prognosis must be guarded in those patients who have a lesion with histologic features of malignancy, and the prognosis in the individual case cannot be predicted, as it almost never can be in neoplasms in any situation, on the basis of histologic appearance alone. Lilienthal's case rather dramatically illustrates the truth of this statement.

No mediastinal tumor produces a sufficiently distinctive clinical or roentgenologic picture to permit a consistently accurate pathologic diagnosis. Many of these tumors are malignant, others have malignant potentialities, and all should be removed surgically unless a definite contraindication exists.

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MESENCHYMOMA OF THE PLEURA

A Case Report

EDWIN F. ALSTON, M.D.,* AND DONALD L. PAULSON, M.D.†
FORT SAM HOUSTON, TEXAS

REPORTS of primary pleural tumors are numerous, but observations and interpretations of these tumors continue to raise many perplexing questions.

Primary tumors of the pleura have presented an extremely varied histology (Robertson,[1] Stout[2]). They have been described as (1) combined sarcoma and carcinoma (sarcocarcinoma), (2) sarcoma, and (3) carcinoma. These differences in histology have led to extreme difficulty in relating the tumor to a specific tissue of origin. The elements most commonly considered as possible precursors of the various pleural tumors have been (1) the subpleural lymphatic vessels, (2) the subpleural connective tissue, and (3) the serosal lining cells or pleural mesothelium.

It can be readily surmised from these considerations that there are difficult problems confronting the pathologist in the identification and classification of pleural tumors in regard to histology and origin. Because classification depends partially upon accumulated observations, we are reporting a primary pleural tumor which has aroused considerable interest because of its peculiar position in the right upper interlobar fissure, its strange histology, and its probable histogenesis.

CASE HISTORY

R. S., an asymptomatic 51-year-old white man, a veteran of World War I, was admitted to the Brooke General Hospital on Jan. 14, 1946, having been referred to one of us (D. L. P.) by Dr. R. G. McCorkle of San Antonio, because of a tumor in the right lung. This tumor was first observed in 1942 when chest plates were taken during an attack of influenza associated with pain in the chest. At this time it was thought to be a cyst of the right lung. The patient remained asymptomatic, but a repeat chest x-ray examination in 1945 revealed that the mass had doubled in size. He was, therefore, admitted to the Brooke General Hospital for further observation and treatment. He had no complaints; he gave no history of cough, sputum, or fever. The patient's past history revealed that he had had pneumonia three times as a child. The last attack was in 1912, when he apparently had an associated empyema on the right. Subsequent to this time he had had influenza about once a year for the past four or five winters, but he had had no other complaints referable to the chest.

Physical and laboratory examinations were noncontributory.

Roentgenograms of the chest on Jan. 16, 1946, revealed a discrete oval shadow in the right mid-thorax measuring 6.5 by 9.0 cm., located in the anterior half of the thorax (Fig. 2). The margin was smooth and sharp. The appearance was interpreted to be that of a retention cyst. The rest of the chest was apparently normal.

From the Departments of Pathology and Thoracic Surgery, Brooke General Hospital.
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*Formerly Chief of Pathology Section, Brooke General Hospital; now Assistant Resident in Medicine, University of California Hospital, San Francisco, 22, Calif.

†Formerly Chief of Thoracic Surgery, Brooke General Hospital; present address: Department of Surgery, Southwestern Medical College, Dallas, Texas.

A. *B,* *C.*

Fig. 1.—*A*, Roentgenogram made in 1942. *B*, and *C*, Roentgenograms made in 1945 revealing the tumor in posteroanterior and right lateral exposures situated anteriorly. The tumor has increased in size.

A bronchoscopic examination revealed narrowing of the orifices of the bronchi to the middle lobe and the dorsal division of the lower lobe of the right lung.

Bronchography revealed minimal cylindrical bronchiectasis involving the basal portion of each lower lobe. There was nonfilling of the right middle lobe including the mass previously visualized. There was slight displacement of the bronchi about the mass.

Surgical exploration was advised, and on Feb. 19, 1946, one of us (D. L. P.) performed a thoracotomy and found a mass in the interlobar fissure completely surrounded by the right upper and middle lobes. The tumor was nodular, solid in consistency, and well encapsulated. The capsule was dissected free from the visceral pleura covering the upper and middle lobes to which it was markedly adherent. The tumor apparently derived its blood supply from the parenchyma of the middle lobe. Two moderate-sized vessels from the midde lobe were encountered during the dissection of the capsule. The tumor was completely removed with the capsule intact.

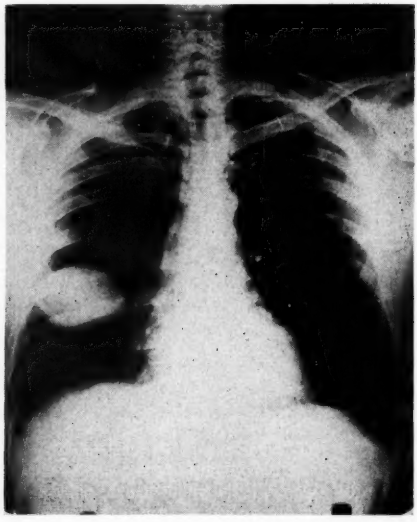


Fig. 2.—Posteroanterior roentgenogram of the chest revealing a discrete oval shadow measuring 6.5 by 9.0 cm., situated anterior in the right mid-thorax. (Brooke General Hospital, U. S. Army, Neg. 46-1444.)

The postoperative course was uneventful. The patient has been observed intermittently since his discharge from the hospital. He is in good health and has no complaints. Repeated examinations have revealed no evidence of recurrence of the tumor.

PATHOLOGY

The specimen consisted of a firm, nodular, slightly flattened oval-shaped mass measuring 10.3 by 3.5 by 7.5 cm. The external surface was completely covered by a thin, dull reddish brown capsule which was slightly roughened by numerous fibrous tags. The capsule bulged over nodules measuring from 0.1 to 4.5 cm. in diameter. The surfaces of these were relatively smooth, grayish white, and homogeneous. The intervening tissue was dark reddish brown connective tissue (Fig. 3).

The histology of the tumor as well as the cytology showed striking variations. The nodular areas observed grossly differed from the intervening tissue only in the degree of cellularity. The nodules themselves varied somewhat in cellularity. Some showed closely packed cell nuclei (Fig. 4, *A*). These were round to oval in shape and contained irregular

networks of chromatin. A few contained nucleoli. Nuclear membranes were well defined. The nuclei varied slightly in size and shape. Many were quite pyknotic. A few mitotic figures were present. Cell borders were poorly defined. The cytoplasm was clear or vacuolated. The extremely cellular areas contained very little stroma. The less cellular areas showed a moderate amount of pink-staining fibrillar material running between the nuclei, staining as collagen. Some of this tissue was almost acellular (Fig. 4, *B*).

Numerous portions of the tumor were extremely vascular (Fig. 4, *C*). In areas where the amount of stroma predominated over the number of cells the perivascular areas were surrounded by a dense mantle of tumor cells. There were numerous spaces varying in size, filled with blood, and lined by tumor cells (Fig. 4, *D*).

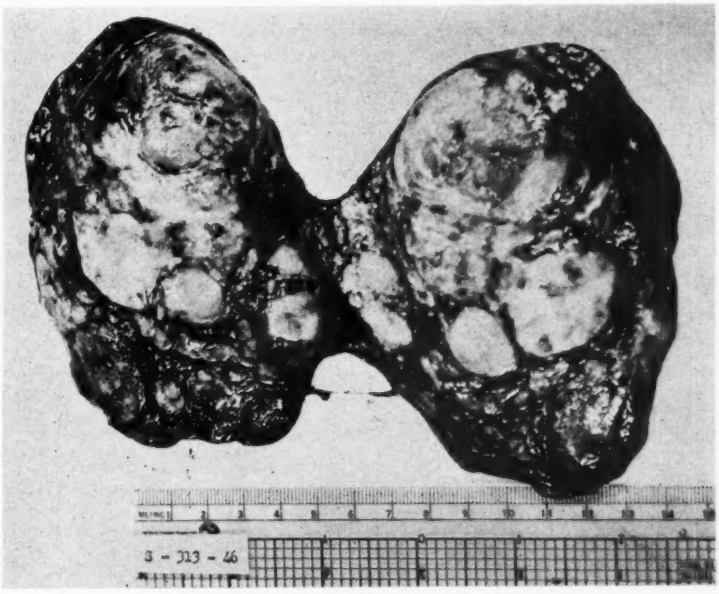


Fig. 3.—Gross appearance of the tumor. The mass was oval in shape and was made up of grayish white nodules of variable size separated by dark reddish brown connective tissue. (Brooke General Hospital, U. S. Army, Neg. 46-544.)

Several of the smaller nodules were made up of extremely large giant cells of irregular size and shape (Fig. 5, *A*). These giant cells often contained numerous multilobular nuclei with coarse networks and condensations of chromatin. The cytoplasm of these cells was more or less amphophilic and often contained very large, clear, well-circumscribed vacuoles. These vacuoles stained positively for fat with Scharlach R. The intervening stroma was made up of pale pink-staining homogeneous material.

The appearances thus far described characterized most of the tumor. However, there was one small area adjacent to the pleural surface which presented an entirely different structure. Here the histology consisted of numerous branching tubular structures lined by cuboidal cells showing round darkly staining nuclei and abundant neutrophilic cytoplasm (Fig. 5, *B*). The tubular structures were separated from one another by connective tissue stroma similar to that described above. Adjacent to this nodule the surface of the tumor was partially covered by intact serosal lining cells which dipped into the connective tissue forming crypts which bore an appearance identical to the tubular structures of the nodules described above (Fig. 5, *C*). Elsewhere, the surface of the tumor was also covered by prominent

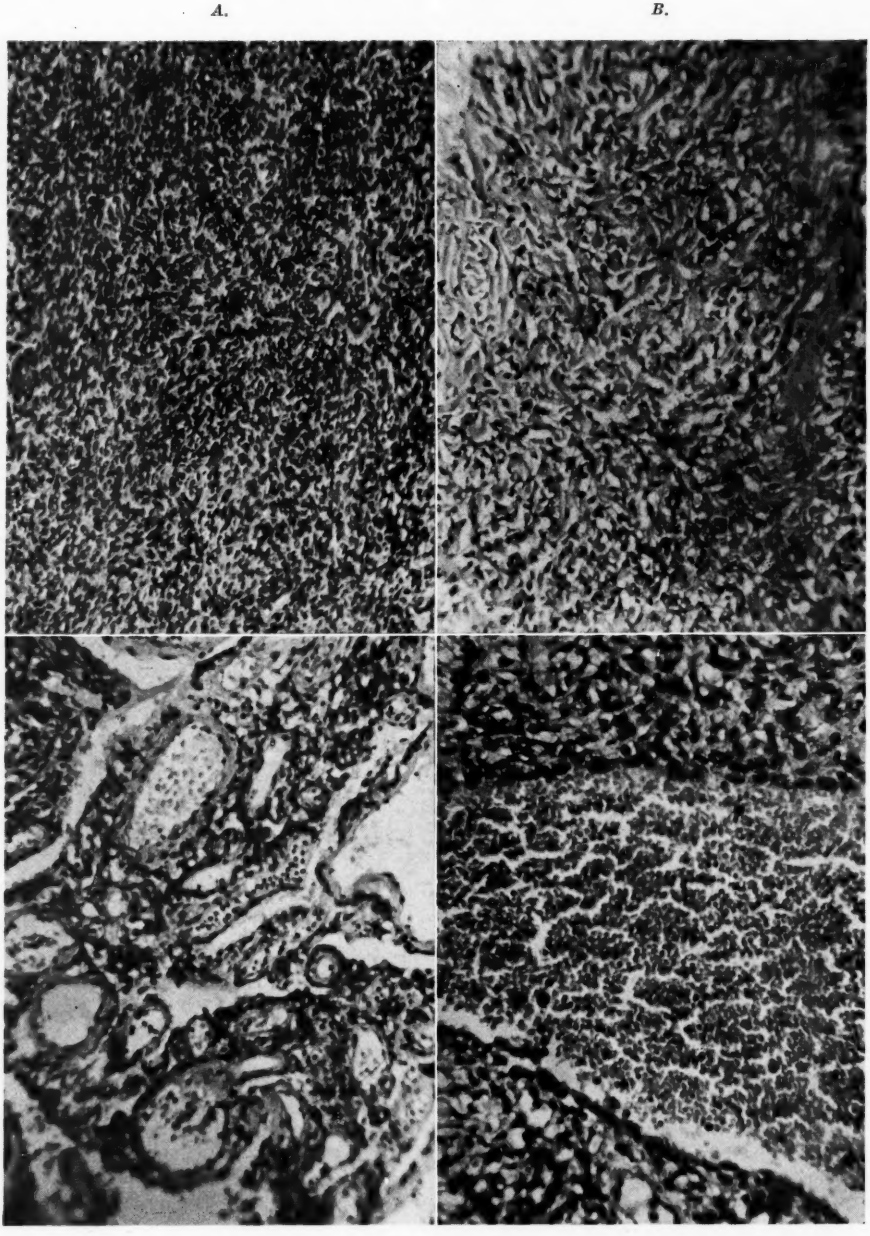
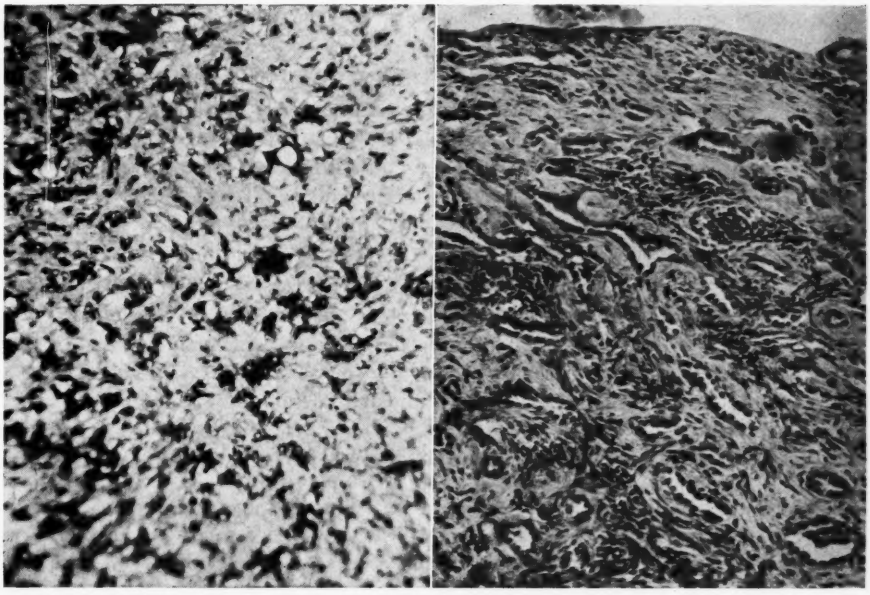
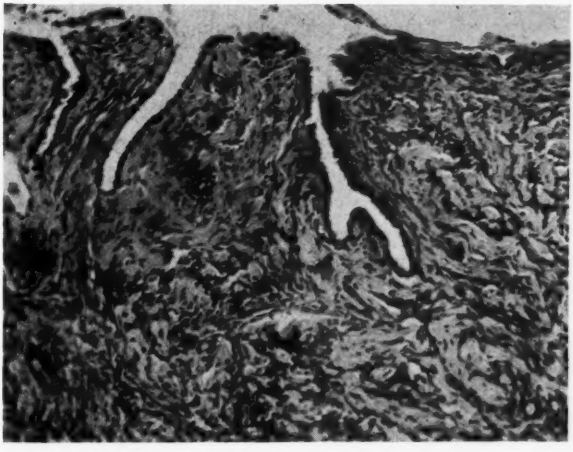


Fig. 4.—Photomicrographs of various sections of the tumor revealing: *A*, marked cellularity; *B*, areas of dense collagen; *C*, extreme vascularity; and *D*, irregular spaces filled with blood cells and lined by tumor cells. (Hematoxylin and eosin ×100.) Photos by U. S. Army Signal Corps.



A. *B.*



C.

Fig. 5.—Other sections of the tumor show: *A*, large multinuclear giant cells with vacuolated cytoplasm (possible lipoblasts); *B*, tubular structures lined by cuboidal cells from the serosal surface of the tumor; and *C*, intact serosal lining cells covering the surface of the tumor and dipping into the substance of the tumor forming crypts which resemble the tubular structures noted in the previous section, *B*. (Hematoxylin and eosin ×100.) Photos by U. S. Army Signal Corps.

intact serosal lining cells which were flat to tall columnar in shape, and orderly in arrangement. In no area was there any evidence that the serosal lining cells actually participated in the tumor process.

DISCUSSION

We believe that this was a connective tissue tumor. None of our observations suggested that this tumor was related to the subpleural lymphatic vessels. The only elements presenting an epithelioid appearance appeared to be nothing more than invaginations of pleural lining cells, which covered the tumor. Since these pleural lining cells—mesothelial cells—did not apparently participate in the tumor, we do not believe that a diagnosis of mesothelioma can be supported.

The microscopic observations indicated various phases of connective tissue differentiation. The numerous bizarre spaces lined by tumor cells and filled with blood appeared to be a part of the tumor process rather than a vascular reaction to the new growth. The unusual vacuolated giant cells had the appearance of lipoblasts.[3] In addition, there was fairly well-differentiated connective tissue showing definite production of collagen, which appeared to be neoplastic rather than reactive. All of these considerations lead to the suspicion that the precursor cell must have been one capable of producing these various elements. It follows, then, that the precursor cell in this tumor must have been the mesenchymal cell.[3]

Sections of this tumor were sent to Dr. Arthur Purdy Stout, who wrote as follows: "I agree with you that the glandlike structures are probably inclusions of pleural mesothelium and probably not an integral part of the neoplasm, since they are confined to only one small area near the pleura. This tumor is not exactly like the one described by Dr. Murray and myself[2] because it seems to have a greater variation in the mesodermal structures produced. As you quite justly remark, there are portions of this growth which look very much like neoplastic blood vessels and they are so numerous and bizarre that I cannot fail to suppose that they are part of the neoplastic growth. The area where the foamy giant cells are found suggests quite strongly the appearance of liposarcoma. The giant cells seem to me to be more than mere phagocytes; rather they are more probably lipoblasts. The amount of collagen and reticulin in this tumor is remarkably varied in quantity and thickness; moreover the arrangement of fibers and cells is very bizarre and does not reproduce the customary appearance of fibrosarcoma. If we are correct in supposing that this is a mesoblastic tumor which differentiates into lipoblasts, vascular structures and bizarre mesenchymal structures in different areas, then I think that this tumor belongs to a special variety of which I have been accumulating examples with the idea of classifying them all under the term 'mesenchymoma.' I know that this term has been used already with regard to ovarian neoplasms by Novak[4] but it has not met with general acceptance as applied to the ovary, and I think it can be used with much greater accuracy with a tumor such as this and others like it which, in addition to the structures seen in this tumor, also form atypical bone and cartilage."

Our final interpretations are that this tumor represents one which has differentiated into several types of connective tissue, and for this reason must have arisen from a multipotent primitive connective tissue cell, the *mesenchymal* cell (according to Dr. Stout). In multiple sections we were unable to recognize any participation in the tumor on the part of mesothelial cells, and for this reason see no indication to attribute the origin of the tumor to these cells. We realize that our lack of observation of mesothelial involvement does not completely rule this out as a possibility. It seems more probable to us however that this tumor arose in the subserosal connective tissue from the mesenchymal cell, occurring there either through lack of prior differentiation or through reversion of mature cells to this more primitive type.

SUMMARY

An asymptomatic 51-year-old white man presented himself for removal of a thoracic tumor which had been discovered incidentally on x-ray examination of the chest four years previously. During this interval of four years it had doubled in size. The tumor was removed. Pathology studies revealed a tumor made up of diverse connective tissue elements which suggested that its origin was from a multipotent mesenchymal cell. It apparently belongs to that group of tumors classified by Stout as mesenchymomas.

Two years after removal of the tumor, the patient is living a normal life, and is well. There is no evidence of recurrence of the tumor.

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USE AND ABUSE OF BRONCHOSCOPY IN ALLERGIC ASTHMA

GEORGE L. WALDBOTT, M.D.
DETROIT, MICH.

BRONCHOSCOPY is employed in bronchial asthma mainly for the purpose of differentiating it from other types of wheezing. Early advocates[1] of therapeutic bronchoscopy in allergic asthma observed that aspiration of the characteristic tenacious mucus benefits some patients considerably while in others in whom there is little secretion in the bronchial tubes, no improvement ensues. This experience is now shared by many.[2]

In 1938, I reported[3] that bronchoscopy had been a lifesaving procedure in several instances. It was then suggested that all asthmatic patients in a moribund state should be given the benefit of this treatment. Although an increasing number of clinicians[4] concur in this view, there is considerable reluctance on the part of both bronchoscopists and allergists to employ the procedure in an extreme emergency.* For this reason it was attempted to review the records of therapeutic bronchoscopies in 112 patients with allergic asthma with the view of setting up distinct criteria for the indication and contraindication of bronchoscopic therapy.

PATHOGENESIS OF ASTHMA

Before approaching the subject proper, brief reference to the mechanism of asthmatic attacks must be made. Asthmatic wheezing is effected by air passing through partially obstructed bronchi. This obstruction is caused by mucus as well as by bronchospasm which, as recent knowledge suggests, are due to histamine elaborated from the antigen-antibody reaction. From clinical experience it appears that the mucus becomes thicker in consistency and its expulsion more difficult, the more protracted the condition.† Wheezing and cough are relieved when some of the mucus is expectorated. Conversely, when elimination is interfered with (e.g. opiates), the attacks become more severe. An unusual degree of dryness of the respiratory surfaces further tends to make the mucus sticky and adherent to the bronchial walls. In this state the bronchial dilation brought about by the action of epinephrine and aminophyllin no longer suffices to loosen it up sufficiently for expectoration. These drugs are no longer effective (epinephrine-fast). The gluelike material behaves like a foreign body. It constitutes a check valve to the portion of the lung distal to it, allowing the air to enter during inspiration, but trapping it during the expiratory phase of the respiration.

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*This was recently brought out when three bronchoscopists refused to carry out the procedure in one of my patients dying from asthma, because they considered his condition "too far advanced." A fourth consultant finally performed the bronchoscopy, which was immediately followed by a dramatic recovery after 120 c.c. of thick mucus were aspirated from the bronchi.

†The changes in the appearance of the expectorated material resemble those seen in hay fever in which, at the beginning of the season, the nasal and sinus mucosa secretes a copious, watery fluid, that becomes thicker and purulent later on.

INDICATIONS

With this in mind, the principal reason for a therapeutic bronchoscopy in allergic asthma is to remove the thick, tenacious mucus which accumulates in the bronchial tree and interferes with respiration.

In practice, bronchoscopy should be employed: (1) To prevent a moribund patient from becoming asphyxiated through the accumulation of the mucus; (2) to break up a chronic asthmatic state—so-called status asthmaticus—regardless of its severity; (3) to remove a single mucous plug which, through complete obstruction of a bronchus, has produced partial or total pulmonary atelectasis; (4) to dilate strictures of the bronchi which follow inflammatory changes of the bronchial mucosa; (5) to remove mucous secretion from bronchiectatic areas.

1. *Emergency.*—Eight patients in this series of 112 (Table I) were in a moribund state. Either following sudden onset, or developing gradually, their condition had deteriorated in such a manner that it had become refractory to all medication. The expectoration, which had been without difficulties at first and had yielded copious and viscid material, had gradually "dried up" and become very laborious. In all but one patient (Case 2, to be described later) the main bronchi and secondary ramifications of the bronchial tree were completely obstructed by mucous plugs. After the removal of between 30 to 60 c.c. of this material through aspiration and lavage with saline solution, the asthma subsided.

TABLE I. RESULTS OF 144 BRONCHOSCOPIES IN 104 PATIENTS*

	TOTAL	EXCELLENT	GOOD	NO EFFECT
Emergencies	8 (11)	7 (10)	--	1 (1)†
Chronic asthmatic state including:	96 (132)	8 (8)	50 (75)	38 (49)
Bronchiectasis			Indefinite	
Atelectasis	4 (5)	3 (3)	--	1 (2)
Bronchostenosis	4 (6)	3 (3)	1 (3)	--
Total	104 (144)			

*While some of these patients remained free from asthma following the bronchoscopic treatment, the results represent only the short-term response to the treatment since permanent improvement might be attributable to measures employed previously.

Number of bronchoscopies indicated in parentheses.

†Case 2.

In one case (a 16-year-old girl), bronchoscopic treatment appeared to be lifesaving on four occasions. When, on admission to the hospital during another such extreme attack, the bronchoscopist was not immediately available, the patient died.

2. *Status Asthmaticus.*—By far the majority of bronchoscopies were carried out for the purpose of breaking up a chronic, not necessarily severe, state of asthma which did not yield to other modes of treatment. If the sputum of a chronic asthmatic patient presents bronchial casts, if each coughing spell results in severe wheezing which is somewhat relieved upon expectoration, or if there is evidence that "the mucus does not come up any more," bronchoscopic treatment should be considered. Upon endoscopic inspection, there is, in addition to the obstructing mucus, considerable narrowing of the bronchial

lumen; bronchospasm may actually be so severe that it may simulate a cicatricial stenosis; collapse of the posterior walls of the trachea and bronchi may be noted on expiration; the bronchial mucosa exhibits acutely inflamed areas which are interspersed with normal appearing ones. One hundred thirty-two bronchoscopies were performed on 96 patients (Table I). In eight, a single bronchoscopic treatment was followed by complete and lasting relief from asthma, and fifty additional patients improved considerably following one or more bronchoscopic treatments; the remaining thirty-eight experienced little or no benefit. Among the former there were several individuals in whom the asthma was aggravated, or induced, by psychogenic factors. Here marked bronchospasm was noted, but little or no mucous secretion was present in the bronchi. When the mucus is not completely removed through the bronchoscope or expectorated subsequently, patients may relapse into the asthmatic state after initial improvement. In this case it is advantageous not to wait longer than one or two days for a second bronchoscopic treatment in order to remove the mucus more thoroughly.

3. *Atelectasis.*—A single mucous plug may lead to either complete or partial atelectasis of a pulmonary lobe, according to whether a main or secondary bronchus is obstructed. The physical findings of suppression of breath sounds and vocal fremitus cannot be elicited as clearly here as in non-asthmatic individuals because of the marked wheezing throughout the lungs. Localized excessive wheezing about the atelectatic areas is a characteristic finding of diagnostic significance. Complete atelectasis of a single pulmonary lobe is not an uncommon complication of allergic asthma. In one of the four patients in this series the bronchoscopist did not succeed in eliminating the mucus and clearing up the atelectasis.

4. *Stricture of Bronchi.*—In three patients, an exceedingly chronic asthmatic state was accounted for by bronchostricture which originated from inflammation of the bronchial mucosa. Nonproductive cough, suppression of breath sounds and fremitus over the affected area, and febrile episodes due to localized pneumonitis characterize this condition. Here, too, wheezing around the affected areas in excess over that heard in other parts of the lungs is a significant diagnostic sign. X-ray findings are less conclusive than in atelectasis. In contrast to a much larger incidence of this condition suggested by Prickman and Moench,[5] the records of our series revealed only four cases in which bronchostrictures were demonstrated. Three patients with persistent asthma showed complete recovery following a single bronchoscopic dilatation of the stricture.

5. *Bronchiectasis.*—In my experience, permanent bronchiectasis is encountered less frequently as a complication of allergic asthma than the literature indicates. In every patient with protracted asthma one would expect some temporary widening of the terminal bronchi, considering the large amount and the consistency of the mucus found on bronchoscopy in the ramifications of the bronchial tree. Indeed, our experience on several patients bears out the fact that such temporary bronchiectasis is no longer in evidence after the attack has subsided.

If a bronchography with lipiodol is desirable when bronchiectasis is suspected, great caution should be used. Reactions are not uncommon; even exitus from this procedure has been reported.[6] Allergic patients may be sensitive to the contrast material. In other cases, the "crowding" of the oil into a bronchial tree, filled to capacity with mucus, may lead to asphyxiation of the patient.

CONTRAINDICATIONS

Bronchoscopic treatment should not be employed when there is little or no mucous secretion or when the sputum is thin and watery. This is true (1) in asthma of short duration where there is edema of the alveoli which is often followed by pneumonitis;[7] (2) in incipient asthma characterized by a nonproductive pertussis-like bronchitis[7] in which bronchoscopy reveals petechial hemorrhages, and occasionally urticaria-like edema of the bronchial mucosa; (3) in the sudden severe attacks (allergic shock) following injections, ingestion, or inhalation of antigens to which extreme sensitivity exists where thin mucous secretion in conjunction with bronchospasm dominates the clinical picture.

HAZARDS FROM BRONCHOSCOPY

The reluctance of bronchoscopists to avail themselves of this procedure more frequently in allergic asthma can be understood because asthmatic patients are more susceptible to emergencies than other individuals. Sensitivity to, and intolerance of, anesthetics and other drugs administered before and during the operation constitutes the principal source of danger.

Anesthetics.—On several occasions pharyngeal edema was encountered followed by dyspnea immediately after local application of cocaine or pantocain to the pharynx. If such signs of sensitivity to the anesthetic are recognized promptly, epinephrine, applied locally and injected subcutaneously in large doses (0.5 to 1.0 c.c.), supplemented by intravenous aminophyllin and antihistamines will avert disaster. Intolerance to local anesthetics, on the other hand, manifests itself through such premonitory symptoms as flushing of the face, twitching of the muscles of the extremities, extreme nervousness, sensations of "heat" in abdomen, stertorous breathing and, finally, convulsions.[8] Sodium pentothal,* administered intravenously, is considered a potent antidote.

Preoperative Drugs.—Among preoperative medications, allergic patients are particularly susceptible to hazards from opiates. Codeine, morphine, dilaudid, and Demerol, in my experience, have led to aggravation of asthma. One of the patients (Case 2, Mr. W. F., 57 years old) developed marked cyanosis, Cheyne-Stokes respiration, and cardiovascular collapse within ten minutes after the hypodermic administration of ⅙ gr. of Pantopon. Two hours later a bronchoscopy yielded only small amounts of thin mucous secretion; there was no bronchospasm and the bronchial mucosa exhibited evidence of inflammation throughout. The patient died four hours later. The autopsy revealed

*If this drug is employed as a general anesthetic, it should be used judiciously. In a patient (Mr. R. F.) who received an intravenous injection of 5 per cent sodium pentothal preceding the bronchoscopy, spasm of the epiglottis developed which threatened asphyxiation. Under great difficulties the surgeon succeeded in prying open the epiglottis with the bronchoscope and introducing the instrument into the brochus.

bilateral bronchiectasis, pulmonary emphysema, marked edema, and congestion in the liver and spleen. It was felt that this fatality was the result of intolerance of Pantopon.

Endoscopic Medication.—Because of the hazard of sensitization, a warning should be given against introducing drugs into the bronchial tree. We have abandoned the use of cocaine, Argyrol, 2 per cent guaiacol, 10 per cent silver nitrate, 1 per cent mercurochrome, or 1 per cent menthol, which were advocated by Lukens and others.[1] We are also refraining from the use of sulfathiazole solution. Only penicillin and occasionally small doses of epinephrine are employed under the precautions outlined here.

4. *Other Accidents.*—Severe dyspnea and unproductive cough may occur within a short period after the bronchoscopy. This indicates that some of the tenacious material had been freed but is now blocking some of the bronchial passages. A fatality reported by Lell[2] might thus be explained. One should, therefore, be prepared to reintroduce the bronchoscope promptly for another aspiration in this emergency.

A rather unique accident was encountered during a bronchoscopy in a patient presenting a bronchostenosis (Mrs. K. S., aged 36 years). During the attempt to dilate the stenosed bronchus the dilating bougie was locked so tightly by the spastic contraction that it broke off upon withdrawal. The object was later removed uneventfully by thoracotomy. Since this operation, the patient has been free from asthma.

PRECAUTIONARY MEASURES

In order to minimize the hazards described here, the following suggestions are made regarding the technique of the bronchoscopic treatment: Little or no anesthesia should be employed. If the administration of 1½ gr. of phenobarbital before the operation should not suffice, a 2 per cent solution of pantocain may be sprayed into the pharynx. Sodium pentothal is kept in readiness for intravenous use should there be signs of intolerance to the local anesthetic. Before the bronchoscopy, one-half of a 3¾ gr. ampule of aminophyllin is given intravenously and 1/20 c.c. of 1:1,000 epinephrine, subcutaneously, in order to decrease bronchospasm. Another one-half ampule of aminophyllin is held in readiness for administration during the operation should the bronchospasm remain excessive. Oxygen is continuously administered throughout the procedure. Saline solution is injected through the bronchoscope if the mucus is difficult to remove through aspiration. Only if necessitated by persistent bronchospasm, 0.1 c.c. of a 1:1,000 solution of epinephrine admixed to 30 c.c. of saline is instilled into the bronchi. Larger doses may lead to unpleasant retions from the pharmacologic action of the drug.

Before the bronchoscopy, an effort is made to determine by both history and intradermal skin tests whether or not sensitivity to penicillin exists. If it had been given previously, it should be kept in mind that the optimal time interval during which sensitization develops is between two to five weeks. In spite of the fact that its previous administration produced no ill effect, sensitivity to the drug should be reckoned with. A dose of 100,000 units in 20 c.c.

of saline is introduced through the bronchoscopy if warranted by the presence of marked inflammation of the bronchial mucosa.

SUMMARY

1. The chief indication for bronchoscopic therapy in bronchial asthma is the state of emergency which arises from the patient's inability to expel the characteristic thick, tenacious mucus which might lead to asphyxiation. In a moribund asthmatic patient, therefore, bronchoscopy is as obligatory a procedure as the removal of a foreign body from a bronchus or a tracheotomy in a patient about to become asphyxiated from diphtheria.

2. Other purposes of bronchoscopic treatment are the breaking up of a chronic state of asthma regardless of its severity, the relief of atelectasis, the dilatation of cicatricial bronchostricture, and, occasionally, the relief of bronchiectasis in asthmatic individuals.

3. This treatment is contraindicated in asthma of short duration, in asthma associated with allergic shock, and in other instances where there is no clinical evidence of mucous plugs.

4. The main hazards in bronchoscopy are sensitivity to, and intolerance of, anesthetics and medications administered before and after bronchoscopy, as well as medications introduced endobronchially. For this reason, little or no anesthesia is used, and only saline solution is employed for lavage of the bronchial tree.

5. Introduction of antibiotics into the bronchi may be desirable if infection is the dominant cause of the attacks. However, they should be used very judiciously and an attempt should be made to avoid reactions from sensitivity to them.

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BULLOUS EMPHYSEMA

Case Report

Milton Sills Lloyd, M.D.
New York, N. Y.

IN THE entire field of chest diseases, there is no diagnostic entity within which there is more confusion than the group of pathologic states variously placed under the heading of "Pulmonary Emphysema." On a few points, however, there is some agreement, viz.:

1. Large air cysts seen in children are generally looked upon as congenital.
2. The development of bullous emphysema is, necessarily, preceded by the loss, quantitative or qualitative (or both), of the elastic tissue of the lung.
3. Once bullous emphysema has developed, the pathologic change is permanent and irreversible.

The reason for this continued confusion is, no doubt, that bullous emphysema is nearly always seen in its end stages and the etiology, origin, and development can be only deduced or surmised.

Early diagnosis, based upon signs or symptoms, is impossible and can occur only as an accidental finding when radiography is used routinely or for the study of some coexisting or underlying condition. The writer believes that cases discovered in this way should be reported because of the valuable light which they may throw upon this morbid state. Such a case is presented below, in which etiology, origin, development, symptomatology, and disappearance are all recorded. This patient has also been observed for a period of ten years (from age 2 to age 12 years) which provides the necessary time interval to test the stability of the restored lung under normal living conditions. There has been no recurrence.

The clinical story, in this case, is factual. It is contrary to many existing beliefs. The purpose of this paper, however, is not to discuss or reconcile divergent opinions, but to let the record speak for itself.

CASE REPORT

W. B. was a white male infant, 2 years old. Two months prior to admission to hospital, the patient developed chicken pox, followed by measles. The measles was complicated by pneumonia and empyema on the left side. For one week prior to admission, he had suffered from violent fits of coughing, accompanied by dyspnea, due to the large amounts of mucopurulent material in the bronchial tree. On admission to hospital on March 27, 1938, the temperature was 103.2° F., pulse 160, respirations 48. The patient was in distress, with moderate cyanosis. On physical examination, there were dullness and absence of breath sounds over the entire left side and râles were present in the right upper lobe both anterior and posterior. There was a purulent discharge from the right ear. The red blood cells numbered 4,080,000; white blood cells, 24,000 with a predominance of poly-

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morphonuclears. Other findings were noncontributory. An x-ray film of the chest (Fig. 1) showed a massive empyema on the left side with displacement of the heart to the right and an area of consolidation in the right upper lobe. On the day following admission, 100 c.c. of straw-colored liquid were removed from the left pleural cavity, from which hemolytic streptococcus was obtained on culture. Aspirations were repeated on several occasions and one performed on April 5 yielded greenish pus. The patient was given general supportive treatment, including transfusions. He continued to be dyspneic, however, and to cough violently, expectorating purulent material similar to that obtained from the pleural cavity. On April 21, the second x-ray film of the chest was made (Fig. 2). This

Fig. 1. Fig. 2.

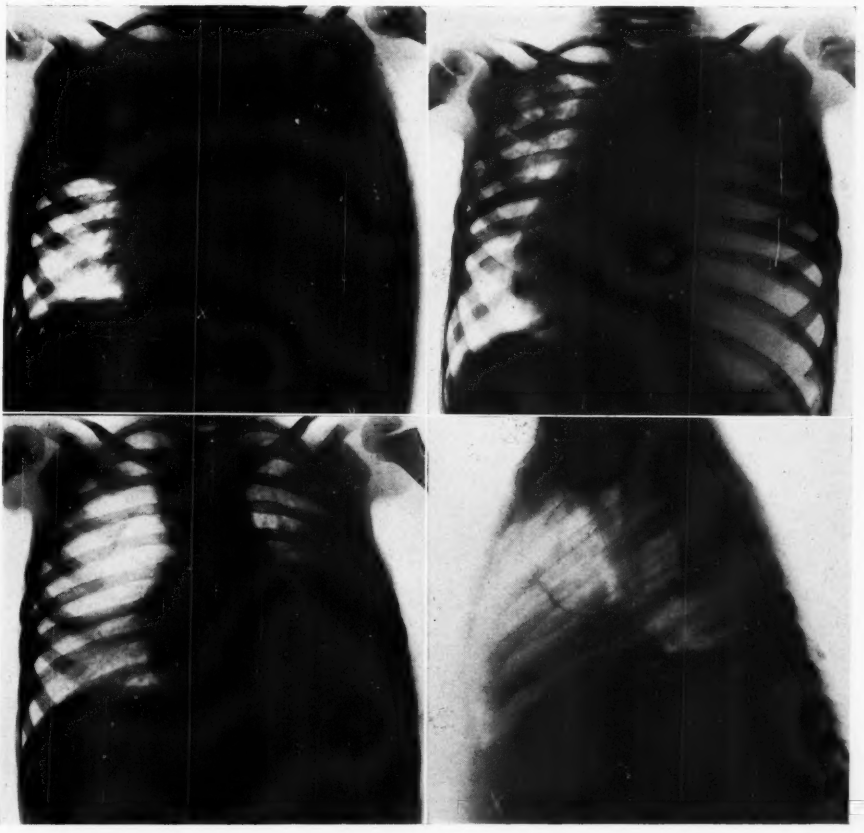

Fig. 3. Fig. 4.

Fig. 1.—Posteroanterior view of the chest taken on March 28, 1938, showing massive effusion on the left and an area of consolidation in the right upper lobe.

Fig. 2.—Posteroanterior view of the chest taken on April 21, 1938, showing tension pyopneumothorax left, resolution of the previously consolidated area in the right upper, with high light over its central portion.

Fig. 3.—Posteroanterior view of the chest taken on May 12, 1938, showing partial re-expansion of the left lung. The high light shown in Fig. 2 is now a definite air sac extending down to the fourth anterior rib.

Fig. 4.—Lateral view of the chest taken on June 15, 1938. The circular outline of the air cyst is clearly seen. A fluid level of the residual empyema is also visible in the posterior costal gutter.

demonstrated a tension pyopneumothorax on the left, total atelectasis of the left lung, displacement of the mediastinum to the right and an irregular high light in the area previously showing a consolidation on the right side.

I first saw this patient in consultation on April 27, at which time a diagnosis of bronchopleural fistula with check-valve mechanism on the left side was made and immediate drainage of the empyema was recommended. A thoracotomy with intercostal catheter drainage was performed on April 29 by the surgeon on service. There was some

Fig. 5. Fig. 6.

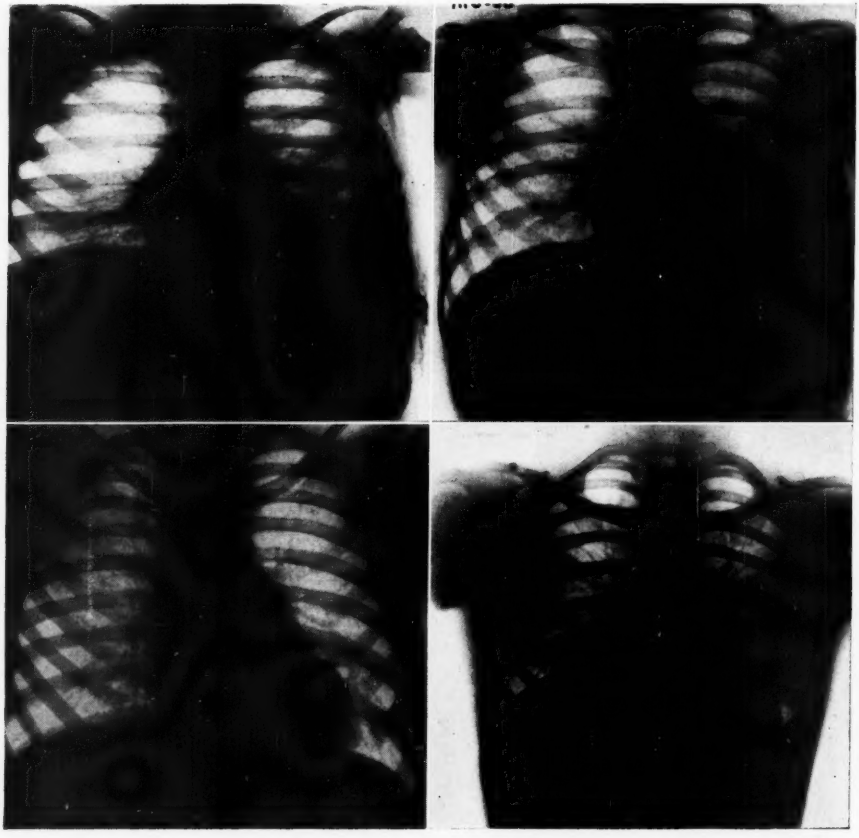

Fig. 7. Fig. 8.

Fig. 5.—Posteroanterior view of the chest taken on June 22, 1938. In this exposure, the air cyst has reached its maximum size from apex to fifth anterior rib, with the entire right lung crowded down upon the diaphragm.

Fig. 6.—Posteroanterior exposure of the chest made on Sept. 2, 1938. The disappearance of cough has been followed by resorption of air in the sac and partial return of the right lung to normal.

Fig. 7.—Posteroanterior view of the chest taken on Nov. 25, 1939. All evidence of the previously existing emphysema has disappeared. Note normal markings in the upper lung field right.

Fig. 8.—Posteroanterior view of the chest taken on June 2, 1948, ten years after recovery. Although the patient has had some "colds" since that time, there is no evidence of emphysema in the right lung. Again, normal lung markings are clearly seen over the right upper chest.

relief following this procedure, but drainage proved inadequate and the patient suffered a return of dyspnea and violent fits of coughing and expectoration. The drainage tube required reinsertion on two or three occasions. A third x-ray film (Fig. 3), taken on May 12, demonstrated a residual empyema on the left with partial re-expansion of the left lung, shifting of the mediastinum to its normal position and a large air sac in the upper part of the right lung. A second thoracotomy was then performed by the surgeon who had taken over service on May 1, with the insertion of a larger catheter in the sixth intercostal space, mid-axillary line. Again, temporary relief was afforded, but cough of considerable severity, with the expectoration of purulent material, continued and, by the beginning of June, dyspnea had again developed. A lateral view of the chest (Fig. 4), dated June 15, shows a clear outline of the developing air cyst on the right with a fluid level on the left posterior costal gutter. The patient was transferred to my care on June 16. The drainage site was changed to the eighth intercostal space in the scapular line, with water seal hook-up. Fig. 5, a roentgenogram of the chest taken on June 22, showed a considerable enlargement in the air sac on the right in spite of a satisfactory diminution in the severity of the cough.

From this point onward, the patient made uniform progress toward recovery. He was discharged and referred to the outpatient department for follow-up on Aug. 3, 1938. A check-up x-ray film (Fig. 6) was taken on Sept. 2, 1938, after injection of Lipiodol into the residual sinus. The air cyst in this examination was reduced to about one-third of its previous volume. The patient was kept under observation and a follow-up x-ray picture of the chest was taken on Jan. 25, 1939 (Fig. 7), which showed complete re-expansion of the left lung and complete resorption of the air in the cystic formation on the right side.

A recent roentgenogram (Fig. 8) taken on June 2, 1948, ten years after the first illness, demonstrated a chest of normal appearance. Particularly notable is the distribution of lung markings in the right apical region over the original site of the air cyst.

SUMMARY AND CONCLUSIONS

A case of bullous emphysema of the right lung is reported, in which etiology, development, clinical course, disappearance, and ten-year follow-up are all recorded.

Observations in this case are at variance with many of the accepted opinions on the disease. A study of the facts presented should, therefore, be of value.

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EXPERIMENTAL OBSERVATIONS ON EMBOLISM OF PULMONARY LOBAR ARTERIES

MASAUKI HARA, M.D., AND JOHN R. SMITH, M.D.
ST. LOUIS, MO.

BECAUSE of the clinical importance of pulmonary embolism, experimental study of obstruction of the pulmonary arterial system has received wide attention. Many of these studies have been concerned particularly with altered cardiorespiratory dynamics and sudden death. Such observations have been extensively reviewed in the past.[1-4]

It is self-evident that simple external compression of the pulmonary arterial circuit may produce critical circulatory block. Haggart and Walker[5] and others[6] have shown that reduction of 60 per cent or more of the pulmonary arterial circulation (by arterial compression) produced a rise of pulmonary arterial blood pressure and a critical decrease in blood flow through the lungs. It is evident also that internal obstruction of the pulmonary arteries, by thrombotic or foreign body emboli, may cause marked impedence of pulmonary flow, and death.[1, 2, 7] On the other hand, some workers have postulated that intense cardiopulmonary reflexes are invoked by lung embolism, and that sudden circulatory failure may result from general arterial constriction (''spasm'') of the pulmonary vascular bed.[4, 9, 10] The postulate is based upon evidence that embolic occlusion may cause a sharp rise in pulmonary arterial tension, a fall in cardiac output, bradycardia, dyspnea, and tachypnea, with marked distention of the right cardiac ventricle and engorgement of the systemic veins. Furthermore, these phenomena have occurred with large or small embolic bodies to the lungs.[4] Some evidence has been presented[4, 11] to suggest that pulmonary vascular spasm occurs with very minute embolization of the ''capillary'' or ''precapillary'' pulmonary bed. Unfortunately, many of the earlier studies entailed the release of foreign bodies from a peripheral vein permitting random embolization of the lungs. From the descriptions of such experiments it is frequently difficult to judge whether the circulatory and respiratory effects resulted from mechanical vascular block or from ''reflexes'' involving pulmonary vascular spasm and peripheral vasodepressor responses.

A step toward more adequate control of effects produced by larger lung emboli is found in the work of Hall and Ettinger.[12] Using dogs, they noted that occlusion of the large pulmonary arteries by balloons, or other objects, produced no notable cardiodynamic effects. Furthermore, electrical or mechanical stimulation of the intimal surfaces of these vessels were likewise without significant effect. Their studies indicate that reflex mechanisms are not produced from emboli lodged in the large pulmonary arteries.

Because of the importance of studying the effects of embolization of the secondary, tertiary, and finer arteries of the pulmonary system the following groups of experiments were performed.

From the Surgical Service, St. Louis City Hospital, and the Cardiovascular Division, Department of Medicine, Washington University School of Medicine.

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METHOD

Dogs of 10 to 15 kilograms in weight were anesthetized with sodium pentobarbital. The thoraces were opened by a transverse incision entailing removal of the third rib, and positive pressure respiration was applied. Systemic blood pressure was recorded by canalizing a common carotid artery using an optical or mercury manometer. Pulmonary arterial tension was conveniently measured by canalizing a branch of the right upper lobar pulmonary artery and using a manometer of choice. All of the animals were heparinized. Under these conditions, the pulmonary arterial blood pressure ranged between 25 and 15 mm. Hg systolic, and 10 and 5 diastolic. The pressure figures are somewhat lower than those frequently recorded in dogs with closed thoraces,[13, 14] but they are within the limits of normal.

The following procedures were undertaken to study the effects of large emboli to the lungs:

1. Balloons made of one-quarter inch Penrose drain were attached to the ends of No. 8 French urethral catheters, using a specially devised balloon attachment. The device was inserted through a puncture incision in the anterior wall of the main pulmonary artery, and the balloon was pushed to a lobar artery of choice in either lung. The catheter was secured by a purse-string suture to prevent leakage. Inflation of the balloon could then be carried out to any given pressure using a conventional mercury manometer.

In order to embolize secondary arterial branches more distally than could be reached with the balloons, ordinary dried pea seeds were introduced singly into the pulmonary arteries through an incision in the right atrial appendage and were permitted to embolize the pulmonary arterial branches at random. A sufficient number of seeds were introduced, one at a time, to produce elevation of pulmonary pressure. The experiment was terminated at any given time.

In addition, "long emboli" were utilized to occlude and distend a secondary vessel more nearly over its entire length. Four navy beans were threaded together by piercing them with a darning needle and thread, providing an embolus which was flexible and 3 to 4 cm. in length. The bean string could be conveniently introduced through a right atrial incision, and could be guided by digital pressure into the right or left pulmonary branches and thence into a secondary vessel. Position of the string was verified by autopsy after dispatch of the animals.

2. Distention, *without occlusion,* of secondary pulmonary arteries was accomplished by use of an instrument similar to that of Hall and Ettinger[12] and of Megibow and associates.[2] Our instrument (see Fig. 1) was of small size and of sufficient flexibility to be easily inserted into a lobar artery. Insertion of the device was through a puncture in the anterior wall of the main pulmonary artery utilizing the technique for the introduction of the catheter-balloon instrument.

3. Obstruction of the finer distal branches of the pulmonary arteries, using small foreign bodies, was accomplished by insertion of a No. 8 French urethral catheter into a lobar vessel. Foreign bodies of glass beads (1 mm. in diameter) and poppy seeds (0.5 mm. in diameter) were placed in the open ends of the

catheters; these bodies were washed into the artery by small draughts of physiologic saline solution until the lobar artery was firmly impacted.

The occurrence of marked, generalized pulmonary vascular constriction[3, 4, 10, 11] from small emboli is thought to be reflected in a sharp rise of pulmonary arterial tension, a fall of systemic blood pressure, with dyspnea, tachypnea,[9] and bradycardia. These physiologic responses were regarded as the important criteria in these experiments. Accordingly, the carotid arterial and

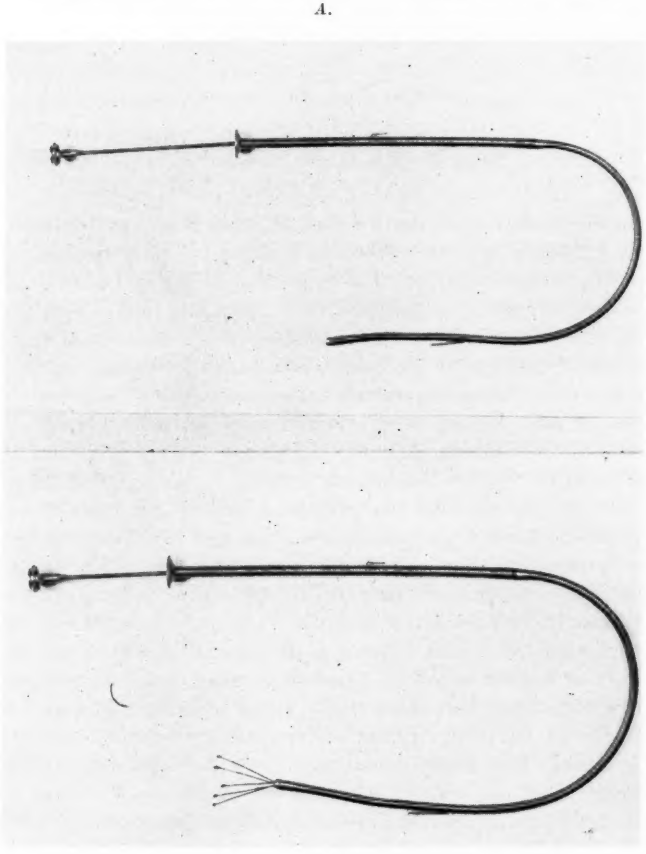

Fig. 1.—Photographs of the spreading instrument: *A*, Showing spreading prongs retracted; *B*, with prongs released. The instrument, made from a camera cable release, is flexible, permitting introduction into pulmonary artery directly, and easy maneuverability to lobar arteries of choice. Flexible cable is 33 cm. long; diameter 3 mm.; the fine spring steel prongs are 23 mm. in length, having a small knob at each tip to prevent tearing of intima and piercing of vessel wall.

pulmonary arterial pressures and heart rate were frequently recorded. In these open-chest preparations, respiratory effort could not be accurately evaluated, although it was possible to note movements of the thoracic wall during severe dyspnea.

RESULTS

Effect of Occlusion and Distention of the Lobar Pulmonary Arteries.—With the catheter and uninflated balloon placed in a lobar artery, no changes in heart rate nor pulmonary and systemic arterial pressures occurred. Subsequent inflation of the balloon likewise produced no changes in cardiovascular dynamics, and no evident respiratory effort. These negative effects upon the dynamics of the circulation persisted with inflating pressures as high as 150 to 300 mm. Hg. It was notable that with inflation of the balloons to 50 mm. Hg or more, the vessel wall, containing the sac, could be seen to be markedly distended. However, if the inflated balloon was placed in either the left or right main pulmonary artery, eliminating the circulation to one lung, a transient rise of pulmonary arterial tension (mean rise of 10 mm. Hg) and a decrease in systemic blood pressure (mean fall of 20 mm. Hg) occurred. The previous pressure levels were restored in three to eight minutes and further circulatory changes were not noted with continued internal occlusion of a main artery. These findings were consistent in nine experiments performed on nine animals.

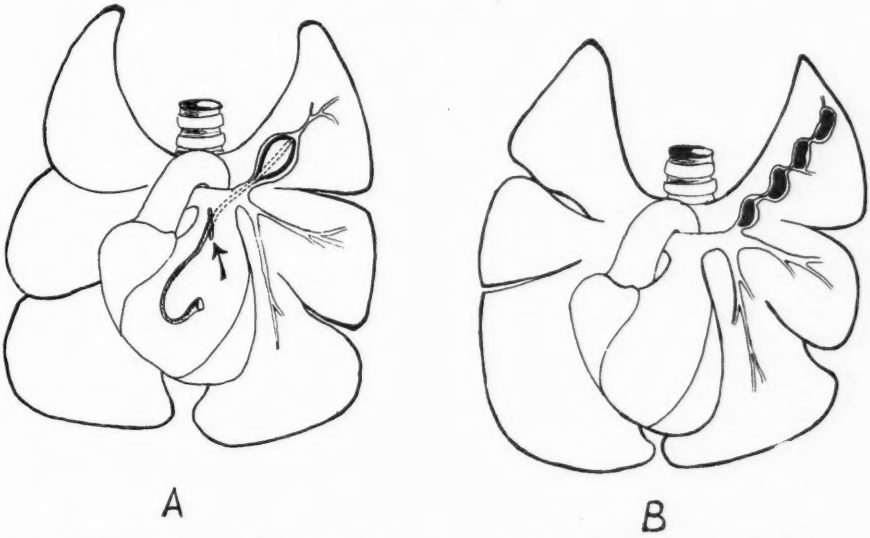

Fig. 2.—Sketches of the approximate positions of foreign bodies used as emboli. *A* shows catheter with balloon occupying left middle lobe artery. The distended balloon causes marked distention of the vessel wall. Point of incision of the main pulmonary artery through which the device is inserted is marked by the heavy arrow. *B* shows position of string of four beans occluding and distending a pulmonary lobar artery. In neither case were cardiovascular dynamics altered by these foreign bodies (see text).

The results of embolism of lobar arteries with single or multiple pea seed emboli were confirmatory of the findings of other investigators.[1, 8, 12, 16, 17] In five experiments performed on five dogs, single occlusion of a lobar vessel by one seed produced no cardiocirculatory changes. Such a lack of response might be anticipated from the similar lack of response with introduction and inflation of a balloon. Similarly, the introduction of fou or five additional pea seeds

provoked no cardiovascular responses. However, it was invariably found that, when the positions of the pea emboli were determined by palpation the seeds had passed to only two or three of the lobar arteries and that each of embolized arteries contained one or more of the seeds. Therefore, critical mechanical block of the pulmonary arterial system did not occur and blood flowed freely to the remaining lung lobes. No changes in cardiocirculatory function were noted. Furthermore, embolization of a lobar artery with the flexible bean strings affected no demonstrable changes in cardiovascular performance although the vessel was occluded and distended over much of its length. The latter was noted in five experiments.

Distention and Mechanical Intimal Stimulation of Pulmonary Lobar Arteries.—In four experiments on four dogs, passage of the instrument for distending the lobar arterial walls provoked no circulatory or respiratory effects. Release of the spreading prongs caused marked visible distention of the vessel walls; however, no changes in tension in the greater or lesser circulations, nor in heart rate, were observed. Furthermore the spreading instrument was manipulated longitudinally through various of the arteries to provide sharp mechanical irritation of the intimal surface. This procedure likewise evoked no alterations in circulatory dynamics.

Embolization of Smaller Vessels of the Pulmonary Arterial System With Solid Foreign Bodies.—Since occlusion and distention by emboli of the main and lobar arteries did not produce appreciable effect upon circulatory dynamics, the bead and poppy seed emboli to smaller vessels of the lungs were next utilized.

In a series of five experiments on five animals, the glass beads (1 mm. in diameter), seventy to eighty in number, were introduced into the catheter, twenty or thirty at a time, and propelled into the catheter and artery by small quantities of saline solution. As the beads were being instilled, no measurable effects on the greater or lesser circulations were detected. Following the procedure, palpation of the lobar artery indicated that the beads were firmly impacted in the vessel. Up to one hour following implantation of the beads, no significant changes in systemic or pulmonary circulatory function occurred.

In a similar group of five experiments, the same procedure was utilized with poppy seeds (Ca. 0.5 mm. in diameter) as the embolizing substance. These seeds were instilled to fill an entire lobar artery. Obstruction with these emboli evoked no changes in circulatory performance, the blood pressures and heart rate remaining unaltered. The lobar vessel of choice was distended and solidly filled with the foreign bodies.

COMMENT

The experimental evidence presented here indicates that neither distention nor occlusion of the main pulmonary arterial vessels, nor of the lobar arteries, provokes recognizable reflex or significant mechanical alterations of cardiovascular dynamics. The results are in general agreement with the findings of others. Haynes and co-workers[11] introduced balloons into the pulmonary arteries of dogs with closed thoraces; inflation of the balloons produced no significant changes of pulmonary or systemic blood pressures, heart rate, nor of electrocardiographic

pattern. Mendlowitz[1] could not explain alterations in circulatory dynamics as reflexogenic effects from long flexible emboli of barium-filled rubber tubing. Other investigators[15-18] have also noted that obstruction of the larger pulmonary arteries using various types of foreign body emboli is usually not suddenly fatal unless widespread mechanical block of the pulmonary circulation occurs.

It is further apparent from these experiments that occlusion of twigs of the pulmonary lobar arterial system to the size of approximately ½ mm. diameter produces no significant effects upon cardiovascular mechanisms if the embolization is confined to one lobe and widespread mechanical block thus avoided.

It would stand to reason, therefore, that sudden death or immediate distortion of cardiovascular function may not be likely to occur following emboli to the larger lobar vessel systems unless critical mechanical obstruction is established. However, it has been found[1, 2] that death in experimental animals may occur several hours after a large pulmonary embolism has been sustained. Under these conditions the mechanism of death is not clear. Megibow, Katz, and Steinitz[2] suggested that thrombi may be generated by large emboli which are then propogated or disseminated to other parts of the lung arterial system. The evidence advanced by Haynes and associates,[11] suggesting that capillary or precapillary embolization may cause violent acute reflex cardiodynamic effects, raises the possibility that following obstruction of large arteries, the finest vessels become occluded, possibly by miliary fragmentation of thrombi originating from such major pulmonary emboli.

SUMMARY

A study is presented concerning experimental pulmonary embolism, using emboli of various size and shape to the secondary and smaller branches of the pulmonary arterial system. It was found that obstruction of lobar arteries themselves and of the finer lobar vessel twigs (to 0.5 mm. in diameter) produce no immediate significant changes in cardiocirculatory dynamics. It was further demonstrated that mechanical irritation of the lobar vessels, and extreme distention of these vessels without occluding them, likewise had no immediate effect upon the circulatory mechanisms. The conclusion seems justified that major pulmonary embolism does not produce acute cardiopulmonary effects if critical mechanical obstruction of the lung circuit is avoided.

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A SCALE FOR RAPID MEASUREMENT OF BLOOD WHICH IS LOST IN SURGICAL SPONGES

ROBERT E. GROSS, M.D.
BOSTON, MASS.

IN EXTENSIVE operations where blood loss is great, it is possible to keep many patients in a safe condition by viewing the amount of blood lost in the field, keeping count of the pulse and blood pressure, and replacing blood in amounts which appear to keep the individual on a reasonably satisfactory plane. While such haphazard methods are sufficient in most instances, it is widely recognized that fatalities or serious complications can result when replacement therapy is inadequately guided. If too much blood is infused the cardiovascular apparatus may be embarrassed or the heart may fail; if too little blood is given, the patient may develop serious or even fatal shock. Visual impressions of the amount of blood which is lost in an operative field may be quite inaccurate, and the excellent studies of Buddington and Taylor,[1] Miller, Gibbon, and Allbritten,[2] and Wangensteen[3] have shown by accurate measurements that the loss from a patient is often much greater than had been expected. It is not practical to conduct accurate studies of hemoglobin loss during all cases of major surgery. However, when blood loss is high it is desirable to have some rough method for guiding the intravenous infusions. For this purpose, Dr. Alexander H. Bill, Jr., and I have reconstructed a scale on which it is possible to weigh sponges after they have been discarded from the field and to determine rapidly the amount of blood which they contain.

In the operative field only dry sponges are employed; these are of a standard, commercial variety which uniformly weigh 8 Gm. Pads are likewise inserted dry; they uniformly weigh 40 Gm. (the equivalent of five sponges). Since the sponges and the pads have uniform size, it is unnecessary to weigh them before they enter the surgical kit. Using sponges of uniform size makes it possible to employ a weighing scale which is fitted with a rapidly adjustable device which can quickly compensate for the number of sponges which are being weighed. Turning this adjustment will allow the scale pointer to indicate directly the number of grams (or cubic centimeters) of blood contained in the soiled sponges.

The scale (Fig. 1) has been remodeled from an ordinary dietetic scale.* It has a dial face which can be turned. The outer rim (1 cm. wide) of this dial has been marked off at intervals of each 8 Gm. (the weight of dry sponges); these markings are made in a counterclockwise direction. The body of the instrument is fitted with a plate carrying the legend "number of sponges" and a central arrow which lies above the rim of the turnable dial face. The platform of the scale has firmly attached to it a pan which will receive the sponges.

From the Surgical Service of The Children's Medical Center and the Department of Surgery of the Harvard Medical School.
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*Manufactured by the Hanson Scale Company of Chicago.

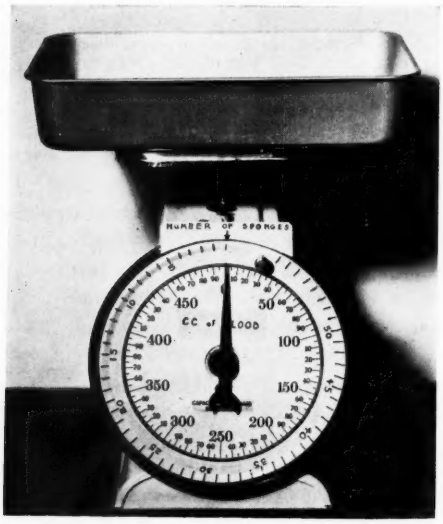

Fig. 1.—Scale for weighing sponges which contain blood. The entire face dial can be rotated around the shaft of the central, main pointer.

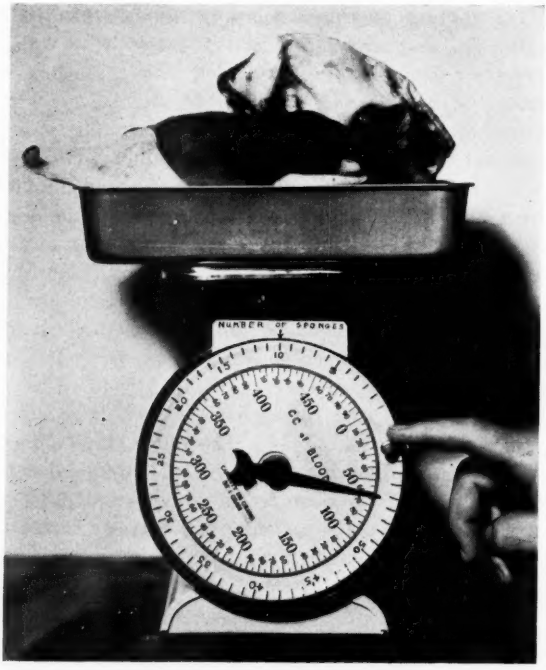

Fig. 2.—The weighing scale in use. Ten blood-soaked sponges have been put in the pan for weighing. With a finger, the face dial is rotated so the figure ten comes opposite to the arrow at the top. The main, central pointer directly indicates that the sponges contain 62 c.c. of blood. (Turning the face dial automatically discounts the weight of ten dry sponges.)

During an operation it is the duty of the circulating nurse occasionally to remove the discarded sponges from the floor bucket and weigh them on the scale which is kept on a side table. If, for instance, ten sponges have been placed in the scale pan (Fig. 2), she simply turns the face dial so that the rim number comes to "10" opposite the arrow at the top of the instrument. *The pointer hand of the instrument will then directly show (on the inner row of numbers of the face dial) the cubic centimeters of blood in the sponges.* These maneuvers take but a few minutes, they require no figuring on the part of the nurse, and they can be carried out in conjunction with her manifold other duties.

It has been my practice to have the circulating nurse keep a rough balance sheet. Each time a load of sponges is weighed, the weight of the blood is added onto the record sheet. To determine the patient's total blood loss at any given moment, it is possible to glance at the bottom figure on this sheet and mentally add to it the amount of blood which resides in the suction-apparatus bottle on the floor. Amounts of blood which are given intravenously are also noted in an appropriate column on the record sheet. This system accomplishes two purposes: First, it allows the circulating nurse to know how much is being lost so that she can replace blood in proper amounts without having to receive instructions from the surgeon or anesthetist who may be having his own difficulties at some particularly critical moment. Second, it permits the surgeon to call at any time for an accounting of the blood balance; he can be told instantly how much has been lost and how much has been replaced. The general method obviously has inaccuracies and it does not account for blood which resides on the drapes, blood which is removed in an excised organ such as a lung, etc. But for practical purposes it is accurate enough; the measured loss indicates the *minimum* amount of blood which must be replaced. As a rule somewhat larger amounts are administered, depending upon the size of the patient, the length of the operation, etc.

This weighing scale was designed for use during operations on coaretation of the aorta. Blood loss from the aorta itself is usually nil or inconsequential, but there may be an astounding leakage from the transected chest wall which has an extremely rich collateral bed in most cases. Large subjects can lose 1,000 to 2,000 c.c. of blood, and in rare instances the figure may be higher. Under such circumstances it is essential to have some simple and rapid method to guide the replacement therapy and keep it within safe limits. For this purpose the scale herein described serves admirably. The implement obviously has uses in other fields of surgery where blood loss is apt to be high and where the use of dry sponges is not objectionable.

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RELATIVE EFFECTIVENESS OF PARENTERAL, INTRATRACHEAL, AND AEROSOL PENICILLIN IN CHRONIC SUPPURATIVE DISEASE OF THE LUNG

EDWARD A. GAENSLER, M.D.,* JOHN F. BEAKEY, M.D.,† AND MAURICE S. SEGAL, M.D.‡
BOSTON, MASS.

DIRECT medication of the lung has been practiced for many centuries. With the advent of effective parenteral and oral medication, interest in this type of therapy declined. It was only when certain specific diseases of the lung failed to respond that interest in intratracheal and aerosol therapy was revived. As early as 1920, Winternitz and Smith,[1] in their book on the pathology of war-gas poisoning, demonstrated the inadequacy of general intravascular therapy in the management of lung damage following chlorine and phosgene inhalation, for parenteral therapy did not reach the necrotic, and thereby devascularized, pulmonary epithelium. In asthmatics, the epinephrine-fast state observed with parenteral therapy was frequently overcome by the use of aerosolized preparations of that drug. It was, however, not until the introduction of chemotherapeutic and biotherapeutic agents that aerosol therapy began to assume greater importance in the clinician's armamentarium.

In spite of the widespread use and acceptance of aerosol therapy, several of the basic principles have not been investigated or have been only briefly discussed in the literature. The pharmacodynamics of absorption from the normal lung was reported in a previous study.[2] Penicillin in saline solution was administered to normal male volunteers. One hundred thousand units of crystalline penicillin G potassium were given parenterally, intratracheally, and by aerosol. It was shown that, although the penicillin molecule is readily absorbed into the blood stream from the alveoli, this absorption was notably slower than that following parenteral administration. Blood levels following intratracheal administration did not reach the early high peaks regularly seen with intramuscular injection, but therapeutically significant blood levels were maintained for twice as long a period of time. The more prolonged retention of penicillin within the body following intratracheal injection was further confirmed by the lower urinary excretion. It was shown that aerosolized penicillin solution resulted in blood levels nearly as high as those obtained by intratracheal administration, but persisted for only one-third as long. From comparison of the total urinary excretions of these two methods, it was possible to calculate the efficiency of the aerosol method. Approximately 35 per cent of the aerosolized solution was shown to be absorbed by the pulmonary epithelium.

From the Department of Inhalational Therapy and the Eighth (Thoracic) Surgery Service, Boston City Hospital, and the Department of Medicine, Tufts College Medical School.

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*Assistant Resident, Eighth (Thoracic) Surgery Service, and Research Fellow, Fourth Surgical Service, Boston City Hospital.

†Research Fellow in Medicine, Tufts College Medical School.

‡Director, Department of Inhalational Therapy, Boston City Hospital; Assistant Professor of Medicine, Tufts College Medical School.

In a related study,[3] the effect of various other diluents, as compared to saline, was reported. Neosynephrin and epinephrine, bronchovasoconstrictors, caused higher initial blood levels and the therapeutic range compared favorably with saline as diluent. No irritation of the bronchial tree was encountered and there appears to be no contraindication to such diluents for penicillin when their actions on the bronchial tree are indicated. Triethylene glycol and chlorophyll were found to be irritating despite topical anesthesia and no enhancement of penicillin activity was noted. These diluents do not appear to be indicated for intratracheal administration but aerosolized chlorophyll may have a beneficial effect as a diluent for penicillin in the presence of mixed gram-positive and gram-negative infection. Human serum did not alter the absorption pattern and iodized oils as vehicles for penicillin powder were discussed.

The relative effectiveness of many types of apparatus used to produce aerosols is difficult to evaluate. In another study of this series,[4] a critical evaluation of eleven of the most common types of aerosol apparatus was made. The highest and most consistently sustained blood levels were obtained when the Vaponefrin nebulizer was modified to include rebreathing with humidification. Methods for the management of the unconscious patient were described, and it was shown that satisfactory blood levels and urinary excretions can be obtained in such a patient.

The pharmacodynamics of absorption from the lung, the influence of various diluents other than saline, and the best apparatus for the administration of such solutions by inhalation were thus established. It then remained to investigate the effect, if any, which pathologic conditions of the lung may have on fluid exchange from alveoli into the blood stream and vice versa. It is not possible in normal volunteers to establish how much of parenterally administered penicillin reaches the lung. Only in the presence of sputum is material available for evaluating the amount of active agent which reaches the site of pathology. Furthermore, since blood flow is reported to be decreased to portions of lung which are diseased, data concerning the value of parenteral penicillin obtained in normal subjects would not be applicable where abnormal conditions are present.

Volhard introduced the intratracheal tube to medical therapeutics and Meltzer and Auer[5] first made extensive use of it not only for intratracheal insufflation of gases but also for introduction of various solid and liquid substances into the bronchi. As early as 1894, Ribbert[6] described the deficient blood supply of the late inflammatory lesions of the lung. The demonstration of the ineffectiveness of intravascular therapy, because of impaired circulation in the late pneumonic lung, contrasted sharply with the dense impregnation of exudate in such lung by dye injected intrabronchially.[7] Direct medication of this organ was thus suggested as an efficient therapeutic route. World War I interrupted these studies, but in 1920 interest again centered on intratracheal administration for the treatment of war-gas poisoning. Winternitz and Smith[1] studied the effects of pulmonary irrigation and intratracheal medication in the treatment of such poisoning. They demonstrated

the relative rapidity with which physiologic salt solution was absorbed from lungs of normal dogs after intratracheal insufflation. Small quantities, such as 30 to 50 c.c., disappeared within forty-eight to seventy-two hours. Administration of phenolsulfonphthalein by various routes demonstrated an appreciably lower rate of absorption (two-hour recovery) following intrapulmonary administration (51.1 per cent) than obtained after intramuscular (72.5 per cent) or intravenous (78 per cent) injection.

Acute inflammatory disorders, such as pneumonia, acute bronchitis, or acute lung abscess, ceased to be major therapeutic problems with the discovery of chemotherapeutic agents. The failure of chronic, purulent, nontuberculous disorders of the lung to respond to parenteral administration of these agents was observed relatively early. Interest in aerosol and, to a lesser extent, intratracheal therapy was, therefore, stimulated. The wealth of clinical evidence for successful aerosol management of various suppurative disorders of the lung quickly and firmly entrenched this mode of therapy in the management of such diseases.[8, 9, 10]

Intratracheal therapy has also been described, but no critical, clinical evaluation has been made. There have been relatively few laboratory demonstrations of the efficacy of such direct medication to the lungs. White and associates,[11] in their extensive study on the prevention of postoperative empyema following lung resection, demonstrated complete absence of penicillin in the bronchial secretions of two patients who received prolonged intramuscular therapy. Bobrowitz and co-workers[12] assayed several samples of sputum following intramuscular administration and could demonstrate only slight penicillin activity in one sputum on only one occasion.

Intratracheal therapy has not had extensive clinical use. Endoscopic insufflation of powdered sulfonamides achieved relatively good results as compared to parenteral therapy when used alone.[13, 14] It appeared, however, that the chief benefit obtained was the reduction of granulation tissue and consequent reduced bleeding tendency. The instillation of liquid sulfonamides has been attempted but found to be large ineffective because of inactivation by para-aminobenzoic acid present in the pus. May and Floyer[15] were the first to describe the treatment of bronchiectasis with intratracheal instillation of penicillin. Under Decicain transcricoid topical anesthesia, 10,000 units of penicillin in 5 to 8 c.c. of water were injected through the cricoid cartilage. Twelve hours later, 10 to 100 units of penicillin per c.c. of sputum were demonstrated. Penicillin activity was detectable in the sputum up to twenty-four hours. Kay and Mead[16] used this type of treatment by the indirect laryngoscopic method without topical anesthesia in ninety-three cases of chronic infections of the lung and bronchi. With a laryngeal cannula, they injected 250 to 50,000 units of penicillin during deep inspiration; patients noted a taste of penicillin for several hours. Ulcerative tracheobronchitis and minimal bronchiectasis responded very well. Moore and Thompson[17] used intrabronchial instillations of penicillin and sulfonamide solution in conjunction with bronchial lavage with great benefit in a case of severe bronchiectasis. Bobrowitz and associates[12] clinically compared intratracheal, aerosol,

and intramuscular penicillin in twelve patients with bronchiectasis. They noted maximum benefit in four to six days after intratracheal administration of 100,000 to 150,000 units of penicillin in 10 to 20 c.c. of saline twice a day with topical anesthesia. Several weeks were required before maximum benefit was noted with the aerosol and intramuscular route. The dosage aerosolized was inadequate, however. After intratracheal administration, high blood levels, a 30 per cent total urinary excretion, and considerable penicillin in the sputum were noted. Penicillin was further demonstrated in the sputum for eight days and in the urine for three days. Using only one-fourth to one-sixth as much penicillin daily by the aerosol route, they were nevertheless able to recover 13 units per c.c. from the sputum and 1.8 units per c.c. from the urine; only traces of penicillin were detectable in the blood in two cases and none at all in three cases. On the basis of these low blood concentrations they concluded that not all aerosolized penicillin entered the lungs. Alarcon[18] obtained dramatic results in the treatment of lung abscess by bronchoscopic and direct tracheal instillation of penicillin. Topical use of penicillin solutions has also been found beneficial in the treatment of tracheotomy wounds, the postlaryngectomy state and acute laryngotracheobronchitis.[19] Administration under fluoroscopic control of penicillin suspended in heavy iodized oil has been suggested for the treatment of abscess cavities.[20] It appeared to us that repeated injection of a heavy oil in suppurative conditions of the lung is undesirable. We have used a very thin, easily absorbed oil (Pantopaque) in similar fashion.[3]

It is, therefore, clear that parenteral therapy alone is unsatisfactory in the chronic suppurative diseases of the lung. The failure of such chemo- and biotherapeutic agents may lie in their inability to reach the site of the lesion.

Having demonstrated the mode of absorption of penicillin from the normal lung,[2, 3] there now remain to be studied: (1) the effect which the chronically diseased lung exerts on this absorption mechanism, and (2) the penicillin concentration in diseased portions of the lung following various methods of administration. Patients with profuse purulent sputum were therefore selected and were given the same amount of penicillin intramuscularly, endotracheally, and by aerosol. The urinary and sputum excretion of penicillin as well as the blood-level curves were then compared.

METHODS

Patients selected had a confirmed diagnosis of some chronic purulent disorder of the lung and raised a large daily volume of sputum. These studies do not represent an attempt at treatment or at clinical evaluation of the results of these individual administrations of penicillin. Routine therapy was resumed after this short period of study. Penicillin was administered intratracheally through a No. 14 French urethral catheter following thorough anesthesia of the tracheobronchial tree with a dilute solution of Pontocaine. The details of this procedure as carried out by us are described elsewhere.[2] This was well tolerated in all instances and no untoward reactions due to the Pontocaine anesthesia were encountered. Unlike the normal volunteers of previous studies,[2, 3] these patients were encouraged to cough as soon as possible after the topical anesthesia had worn off. Cough and expectoration were usually resumed about one-half hour after instillation. Blood was collected at one-half and one hour after administration and every hour thereafter for six to ten hours. Specimens of urine

and sputum were collected one, two, four, six, and twenty-four hours after administration of the penicillin. Sputum and urine were kept on ice during and after the period of collection. The routine was exactly the same when the intramuscular route was employed. For aerosolization the Vaponefrin nebulizer and an attached rubber rebreathing bag with humidification were used. Blood samples were collected for four hours; sputum and urine specimens were collected at the same time intervals following endotracheal administration. Penicillin assays were made by the Rammelkamp dilution method,[21] the limitations and modifications of which we have previously discussed.[2]

CASE HISTORIES AND RESULTS

CASE 1.—T. M., a 59-year-old white laborer, was admitted to the Sixth Medical Service, complaining of an almost uninterrupted productive cough for the past thirty years following a "bronchial catarrh." The sputum, most profuse in the early morning, was described as greenish yellow and occasionally foul smelling. Nine months ago, he first noted some shortness of breath and one week ago he began to feel feverish, experienced mild chills, and noted a dull, steady pain in the right chest, radiating to the back. For the past three days he had suffered from severe headache and "catching" pain in the left chest, worse on coughing and on deep inspiration.

Past history revealed a previous admission to this hospital nine months before for lobar pneumonia, right middle and lower lobe, pneumococcus type 8, and chronic alcoholism with delirium tremens. The patient denied any other episodes of pneumonia or influenza, there were no recent weight loss, night sweats, or hemoptysis, and no family history of, or contact with, tuberculosis. Excessive alcohol consumption for many years was admitted.

Physical examination revealed an elderly, well-nourished, well-developed white man in no acute distress. Temperature on admission was 99.6° F., blood pressure was 120 systolic and 70 diastolic, the pulse rate was 100 per minute and respiratory rate was 22 per minute. There were bilateral immature cataracts, complete anodontia, and marked injection of the pharynx. Examination of the chest showed prolonged expirations and sonorous râles throughout both lung fields. A friction rub was felt in the left axilla. Physical examination was otherwise within normal limits.

Course.—Laboratory examination of the blood, urine, stool, and spinal fluid was normal, as were venous pressure, circulation time, and blood and spinal fluid serology. The sedimentation rate was elevated. The electrocardiogram showed left axis deviation. The patient produced 400 to 800 c.c. of thick green sputum a day. Bacteriologic examination revealed alpha and beta hemolytic streptococci, *Neisseria flava,* and *Micrococcus catarrhalis.* Anaerobic culture did not contribute further. Repeated sputum concentrates were negative for acid-fast bacilli.

Therapy consisted of intensive postural drainage, full doses of parenteral penicillin and aerosol therapy of 50,000 units of penicillin dissolved in 1 c.c. of 0.25 per cent Neosynephrin. Bronchoscopy revealed profuse purulent exudate arising principally from the right middle and left lower lobe orifices. Bronchography confirmed the diagnostic impression of bronchiectasis. There were advanced saccular involvement of the left lower and right middle lobes and lesser involvement of the lingular branch of the left upper lobe as well as the right lower lobe. It was felt that the extent of the involvement, as well as the patient's age, precluded surgical treatment.

On the thirty-seventh day, treatment was interrupted and on the thirty-ninth, forty-first, and forty-third days, penicillin absorption studies were done as outlined above. Previous therapy was then reinstituted. The patient became afebrile on the second hospital day and remained so throughout his two-month hospital course. Somewhat improved, he was then discharged to the care of a Veterans' Facility. His cough at the time was still productive of 60 to 120 c.c. of odorless sputum a day.

Results.—(Table I and Fig. 1.) Blood-level curves following intramuscular administration reveal a quickly reached peak of 1.25 units per c.c. of serum followed by a rapid decline. Therapeutically significant levels were maintained for four hours. Following endotracheal

TABLE I. TABULATION OF BLOOD, URINE AND SPUTUM LEVELS OF PENICILLIN FOLLOWING THE ADMINISTRATION OF 100,000 UNITS OF CRYSTALLINE PENICILLIN G POTASSIUM BY VARIOUS ROUTES IN FOUR CASES OF CHRONIC SUPPURATIVE DISEASE OF THE LUNG

	BLOOD UNITS PER C.C. OF SERUM (HOURS AFTER DOSE)							URINE UNITS PER HOUR (HOURS AFTER DOSE)						SPUTUM UNITS PER HOUR (HOURS AFTER DOSE)						
	½	1	2	3	4	5	6	1	2	4	6	24	TOTAL	1	2	3	4	5	6	TOTAL
Intramuscular.—																				
Case 1	1.25	0.625	0.312	0.078	0.039	0	0	18,750	4,750	12,200	–	250	35,950	0	0	0	0	0	–	0
2	0.625	0.312	0.078	0.039	0	0	0	72,500	10,750	4,750	796	900	89,696	0	0	0	0	0	0	0
3	2.5	1.25	0.156	0.078	0	0	0	22,500	6,250	14,750	–	1,875	45,375	0	–	–	0	–	–	0
4	1.25	0.625	0.319	0.078	0.039	0	0	12,000	8,000	9,000	6,500	100	35,600	–	0	0	0	0	0	0
Endotracheal.—																				
Case 1	0.078	0.078	0.078	0.039	0.039	0.019	0	1,250	1,250	3,500	–	600	6,600	12,300	2,090	105	97	180	0	14,772
2	0.156	0.156	0.156	0.156	0.078	0.039	0.078	1,248	4,688	7,650	2,190	3,000	32,986	13,750	8,125	8,750	4,000	35	24	34,684
3	0.078	0.156	0.156	0.156	0.078	0.039	0.019	7,188	2,370	7,125	–	225	14,538	35,000	38,780	9,690	0	0	–	83,470
4	0.312	0.312	0.312	0.156	0.156	0.039	0.019	8,000	1,250	3,313	499	750	13,812	20,280	4,212	4,514	4,212	0	0	33,218
Aerosol.—																				
Case 1	0.039	0.019	0.019	0	0	–	–	1,170	–	–	–	550	1,720	12,500	3,120	190	0	0	–	15,810
2	0.039	0.019	0.019	0	0	–	–	2,808	370	370	67	2,025	5,068	4,836	1,007	0	0	0	0	5,843
3	0.019	0.039	0.039	0	0	–	–	2,184	1,563	–	–	450	4,197	4,056	–	988	0	0	–	5,044
4	0.156	0.078	0.078	0.039	0	0	0	530	1,250	937	–	16	2,732	7,956	9,048	4,290	2,067	1,989	0	25,350

administration, the peak reached was .08 unit per c.c. of serum which was maintained for two hours, the curve was much flatter and therapeutic levels were also maintained for four hours. After aerosol administration, a peak of 0.4 unit was reached after one-half hour, but this significant level was not maintained. Urinary excretions parallel these results. On intramuscular injection, the total excretion was 35 per cent with a very high peak in the first hour. Only 6.6 per cent was excreted after endotracheal injection and it is interesting to note that more penicillin was excreted during the third and fourth hours than during the first and second hours. The total penicillin excretion, following aerosol administration, was 1.7 per cent.

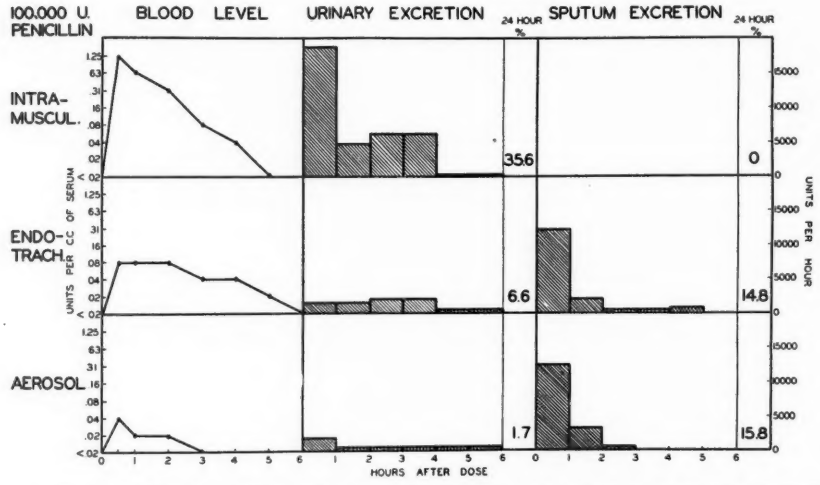

Fig. 1 (Case 1).—Blood levels, urinary excretion, and sputum excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes. T. M., 59-year-old white man with advanced bronchiectasis.

No trace of penicillin was recovered from the sputum at any time following intramuscular injection. Intratracheal injection gave rise to 12,300 units in the sputum during the first hour and at the end of five hours there were still 180 units. An equal amount, 12,500 units, was expectorated during the first hour following aerosol administration and at the end of three hours there were still 190 units per hour in the sputum. A total of 14.8 per cent was expectorated following endotracheal administration and a total of 15.8 per cent following aerosol administration.

CASE 2.—M. R., a 38-year-old Italian salesman was admitted to the Thoracic Surgery Service complaining of chest pain and productive cough. He had been entirely well until one year ago, when he developed what was thought to be pneumonia and was treated at home for several weeks. His cough soon became productive of large quantities of foul sputum. A chest x-ray film at the time revealed a large cavity of the right upper lobe and he was admitted to the Sanatorium Division of the Boston City Hospital. During a three-month observation period all sputum cultures, guinea pig inoculations, and direct smears of concentrates were negative for acid-fast organisms. Follow-up chest plates showed the solitary cavity to be increasing in size, and the quantity of sputum also had increased. A diagnosis of chronic purulent lung abscess was made and the patient was referred to the Thoracic Surgery Service.

Physical examination revealed an emaciated man with an almost continuous profusely productive cough. The only significant findings were those of the right lung which were indicative of a cavity involving almost the entire organ.

Course.—Neither the cough and sputum, nor the low-grade fever were favorably influenced by intensive postural drainage, large doses of parenteral and aerosol penicillin and streptomycin. Bronchoscopy demonstrated much granulation tissue and profuse purulent material in the right main-stem bronchus. Papanicolaou smear of the bronchial aspirations did not show tumor cells and biopsy was negative. In spite of this, it was felt that the most likely diagnosis was excavating bronchiogenic carcinoma. The patient became increasingly ill and lost 25 pounds. After four weeks, he agreed to surgery and a right exploratory thoracotomy was performed. The entire right lung proved to be densely adherent and the hilar structures were enveloped in an inflammatoy mass. The abscess appeared to involve the right upper and middle lobes. Two frozen sections revealed chronic inflammation only, and, in view of the patient's extremely poor physical condition, the thought of pneumonectomy was abandoned in favor of a cavernostomy. The abscessed cavity was packed open and later drained with rubber tubes. Sputum rapidly decreased, he began to gain weight, and was discharged to the Thoracic Out-Patient Clinic. He did relatively well while at home but continued to expectorate moderate quantities of foul sputum. Successive chest plates revealed the right upper lobe to be partly collapsed with a small apical pneumothorax. It was felt, however, that the remaining cavity was too large to close spontaneously and he was readmitted for thoracoplasty.

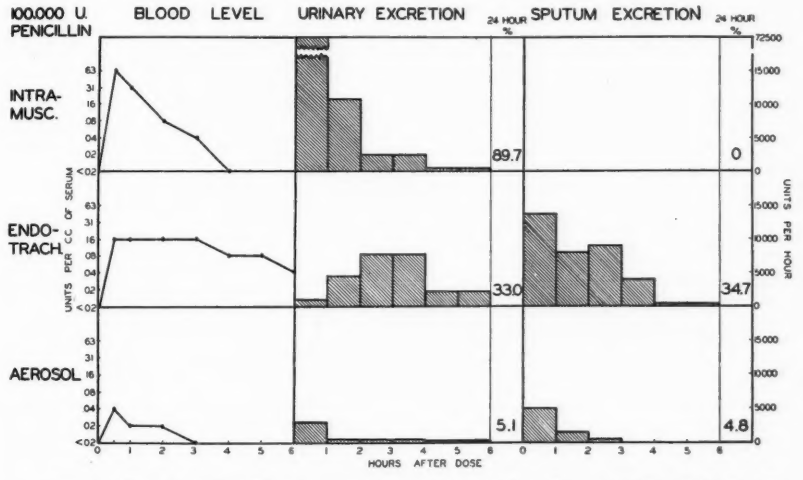

Fig. 2 (Case 2).—Blood levels, urinary excretion, and sputum excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes. M. R., 38-year-old white man with lung abscess of right middle and upper lobe.

During this admission penicillin studies were done. A four-stage thoracoplasty with partial scapulectomy was performed. During the last stage, the posterior portions of the fifth, sixth, seventh, and eighth ribs were removed and the wound was extended into the chronic empyema cavity overlying the abscess and packed wide open. This wound healed rapidly and the patient was discharged eight months after his first admission, the wound completely closed, the cavity collapsed and free of sputum.

Results.—(Table I and Fig. 2.) The blood-level curve, following intramuscular injection, reached a peak of 0.63 unit per c.c. at one-half hour and thereafter declined rapidly. Significant levels were maintained for three hours. Total urinary excretion was 89.7 per cent with a peak of 72,500 units excreted during the first hour. No trace of penicillin could be detected in any of the sputum samples following intramuscular administration. Endotracheal administration produced a peak of 0.16 unit per c.c. of serum after one-half hour, and this peak was maintained for three hours. Therapeutic levels were still assayed at the end of six

hours. Total urinary excretion was 33 per cent. Only 1,248 units of penicillin were excreted during the first hour, while 7,650 units per hour were excreted during the third and fourth hours. During the first hour 13,750 units of penicillin were excreted in the sputum; at the end of six hours there were still 24 units per hour; and at the end of nine hours, 18 units per hour. The patient expectorated a total of 671 c.c. of sputum containing 34,700 units of penicillin during a twenty-four hour period. Following aerosol administration, a significant blood level was observed at the end of one-half hour. The total urinary excretion was 5.1 per cent and 4.8 per cent was expectorated, 4,836 units during the first hour, and there were still 1,007 units during the third hour.

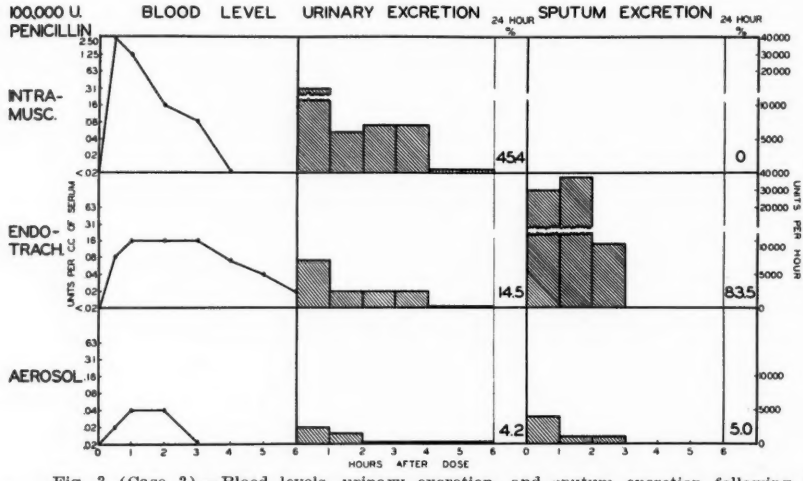

Fig. 3 (Case 3).—Blood levels, urinary excretion, and sputum excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes. T. M., 17-year-old white girl with bilateral bronchiectasis and tuberculosis.

CASE 3.—T. M., a 17-year-old white girl student was admitted to the Thoracic Surgery Service for the sixth time complaining of a chronic productive cough. She was first admitted six years before and treated for right lower lobe pneumonia. She was readmitted three years later because of a cough of three months' duration. At the time, a diagnosis of bronchiectasis of both lower lobes was confirmed by bronchography. Two years ago bronchography revealed severe bronchiectasis of the right middle and lower lobes and minimal involvement of the left lower lobe and lingula. It was felt, at the time, that the patient would be greatly improved though probably not cured by a resection and, consequently, a right middle and lower lobe lobectomy was performed. Convalescence was uneventful and she was discharged greatly improved. She was entirely well for about six weeks while at home and then, following a cold, again developed severe cough and copious sputum. Large quantities of secretions removed from both main stems at bronchoscopy, and x-ray examination at the time, revealed a small shadow at the right apex, and the possibility of tuberculosis was considered. Sputum concentrates, smears, cultures, and guinea pig inoculations in the past and at this admission were negative. The patient was discharged improved following a course of intramuscular and aerosol penicillin. Further bronchograms confirmed bronchiectatic involvement of the left lower lobe and lingula. The present admission again was for productive cough following a cold and sore throat. She also complained of weakness and exertional dyspnea. One day before entry she noted, for the first time, some blood-streaked sputum.

Physical examination revealed a young chronically ill girl. The pharynx and nose were injected, and râles and wheezes at both lung bases were heard. Except for a small mass measuring 1 by 3 cm. in diameter in the upper outer quadrant of the right breast and a

thoracotomy scar, physical examination was otherwise negative. Our studies were carried out and she was then placed on a regular regime of aerosol and intramuscular penicillin on which she improved very rapidly. Bronchograms again demonstrated marked bronchiectasis of the left lower lobe and lingula and slight involvement of the dependent branches of the remaining right upper lobe. Of the first eight sputum concentrates for acid-fast organisms, two were reported positive. Several guinea pig inoculations of sputum were negative but one of several gastric aspirations showed tuberculous infection at the end of six weeks. On strict bed rest and intermittent penicillin therapy, the patient gained 30 pounds and improved greatly. Sputum was reduced to 1 ounce a day. Results of pulmonary function studies and differential bronchospirometry, as well as extent of involvement, precluded further surgery and the patient is awaiting admission to a sanatorium.

Results.—(Table I and Fig. 3.) Following intramuscular injection, blood serum levels reached a peak of 2.5 units of penicillin per c.c. of serum and the levels then quickly fell off, therapeutically significant amounts being detectable at the end of three hours. Urinary excretion was 45.4 per cent with a peak of 22,500 units during the first hour. No trace of penicillin was detected at any time in the sputum following intramuscular administration. After endotracheal administration, the blood levels did not reach a peak until the end of one hour and were then maintained at this level of 0.16 unit per c.c. for three hours. Significant activity was still present at the end of five hours and penicillin was detectable in the blood at the end of six hours. There was excretion of 14.5 per cent of the administered dose in the urine and 83.5 per cent in the sputum, 35,000 units during the first hour, 38,780 units during the second hour, and 9,690 units during the third hour. Following aerosol administration, a peak of 0.04 unit per c.c. was reached at the end of one hour and maintained for one hour. The total urinary excretion was 4.2 per cent and 5 per cent of the total amount administered was expectorated. At the end of three hours, 988 units were still present in the sputum.

CASE 4.—S. G., a 48-year-old, white, single window washer entered the Fifth Medical Service complaining of hoarseness and a cough of six weeks' duration. He stated that he was entirely well until six weeks before admission when he began to notice a rather severe cough, more noticeable at night, at first productive of moderate quantities of white sputum and later of large quantities of thick greenish sputum. He became increasingly fatigued and lost 10 pounds. He denied having had recent contact with tuberculosis, and having night sweats, chills and fever There had never been any frank hemoptysis or blood streaking of the sputum. Shortly before entry, his cough became severe enough to prevent sleep.

His mother died of tuberculosis and one brother of dropsy. The patient's health had always been good except for one episode one year ago characterized by weakness and swelling of both legs; this led to his first admission at this hospital. Discharge diagnosis was chronic Bright's disease with renal edema and cirrhosis of the liver. He left the hospital before further evaluation was possible. Shortly after leaving, the edema disappeared and he felt entirely well until the present episode. He admitted alcoholic intake of 10 to 12 glasses of beer and 1 quart of whiskey every day for the past ten to fifteen years.

Physical examination revealed a well-developed, well-nourished white man in no acute distress. The blood pressure was 130 systolic and 90 diastolic, the temperature was 101° F., the pulse 80 per minute, and respirations 30. Many teeth were absent and the remaining ones were in extremely poor condition. His gums appeared to be infected, and the pharynx was injected. Speech was extremely hoarse; the vocal cords were swollen and edematous but moved equally. Examination of the lungs revealed normal tactile and vocal fremitus and no dullness to percussion but some expiratory wheezes throughout both lung fields with fine crackling râles over the left chest posteriorly. There was some tenderness in the right upper quadrant and the liver edge was found to be 1 cm. below the costal margin by percussion but could not be palpated. Clubbing of both upper extremities was the only other physical finding.

Course.—X-ray examination of the chest demonstrated an area of decreased density, with fluid level, at the base of the right upper lobe posteriorly, consistent with lung abscess. Examination of the urine revealed 1+ albumin and two to four red cells per high-power field. Examination of blood elements and chemistry was normal. Sputum concentrates were ex-

amined for acid-fast organisms and the sediment was injected into two guinea pigs. The sputum was also cultured for acid-fast organisms. All of these examinations proved to be negative. Culture of the sputum revealed alpha and beta hemolytic streptococci, *micrococcus catarrhalis, Neisseria flava, Staphylococcus albus,* and diphtheroids. Anaerobic culture of the sputum did not further contribute. Two blood cultures were negative. Bronchoscopy performed on the twelfth hospital day revealed thick, purulent, grossly blood secretions coming from the right upper lobe orifice, which was completely occluded by tumor and/or granulation tissue. A biopsy taken from this region revealed squamous metaplasia. Papanicolaou smears for tumor cells were negative. The diagnostic impression was putrid abscess of the posterolateral segment of the right upper lobe with possible carcinomatous degeneration, and the patient was transferred to the Thoracic Surgery Service.

Penicillin therapy, instituted on admission, was then interrupted for our usual studies at the inhalation laboratory. Intensive penicillin aerosol and parenteral threapy as well as postural drainage was continued and two further bronchoscopies demonstrated improvement of the local lesion. A biopsy of a right anterior cervical lymph node proved to be negative for metastatic carcinoma. A chest x-ray film on the thirty-ninth hospital day revealed considerable improvement. The abscess had dimnished to almost half its former size and the fluid level had disappeared. There were still occasional temperature rises to about 100° F. On the fortieth hospital day the patient could not tolerate bed rest any longer and left the hospital against the advice of his physicians. Despite appointments and Social Service follow-up, he has never been seen at the clinic.

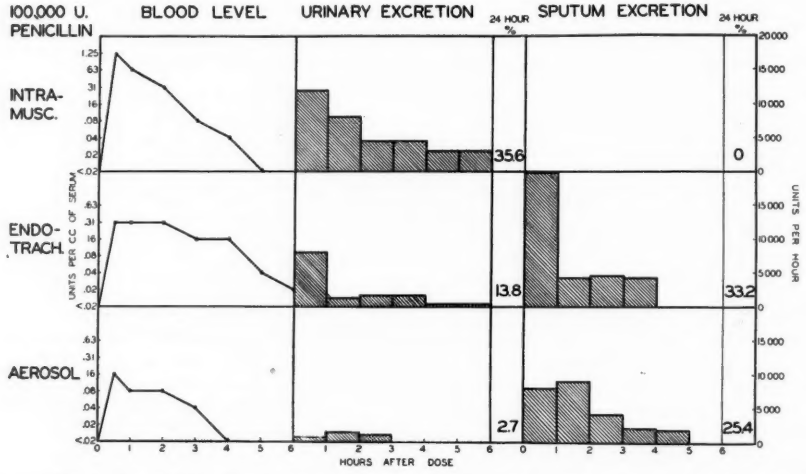

Fig. 4 (Case 4).—Blood levels, urinary excretion, and sputum excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes. S. G., 48-year-old white man with lung abscess of right upper lobe.

Results.—(Table I and Fig. 4.) Following intramuscular injection, blood levels rose to a peak of 1.25 units per c.c. after one-half hour, significant levels being present for four hours. The total urinary excretion was 35.6 per cent and no penicillin was detected at any time in the sputum following intramuscular administration. A peak of 0.31 unit per c.c. was reached one-half hour after endotracheal administration and this peak was maintained for three hours. Significant levels were maintained for five hours and penicillin was still demonstrable in the blood at the end of six hours. The total urinary excretion was 13.8 per cent and 33.2 per cent of the administered quantity was expectorated with a peak of 20,280 units during the first hour. At the end of four hours, 4,212 units per hour were still expectorated. Following aerosol administration, a peak of 0.16 unit per c.c. was reached at the

end of one hour and therapeutic levels were still detected at the end of three hours. The total urinary excretion was 2.7 per cent and 25.4 per cent of the administered dose was expectorated—7,956 units during the first hour, 9,048 units during the second hour, and 1,989 units were still expectorated during the fifth hour.

DISCUSSION

In each of the four patients studied, no penicillin could be detected in the sputum at any time following intramuscular injection of 100,000 units. Following both aerosol and endotracheal administration, significant penicillin activity in the sputum of the same patients was noted for long periods of time. High sputum concentration with the latter routes are to be expected. The inability of intramuscularly administered penicillin to reach the sputum in even the smallest detectable amounts was very striking. These findings are consistent with the clinical impression of the inability of parenteral therapy to cope effectively with chronic purulent disorders of the lung. Roentgenographic and clinical improvement following intravascular therapy in lung abscess and bronchiectasis are probbaly due to resolution of the surrounding pneumonitis rather than to real penetration of the abscess cavities. Direct quantitative measurement of the amount of penicillin which reaches the pulmonary epithelium of the normal or acutely inflamed lung following intramuscular administration is not easily possible. From the successful use of oral and parenteral sulfonamides and penicillin in the acute infectious disorders of the lung, it can be deduced, however, that in the absence of an avascular thickened abscess wall, good concentrations must reach the alveoli. Collection of respiratory-tract fluid from animals by means of a T tube ligated into the trachea[22] has demonstrated as high a concentration of sulfadiazine in this fluid as in the blood for four hours after oral administration. The rigid, thick, avascular wall of the chronic lung cavity must, therefore, represent an efficient barrier to the admission of intravascularly administered penicillin.

From these and other studies, certain conclusions may be made regarding the mechanism of penicillin absorption from the diseased lung. Since parenteral penicillin does not penetrate the purulent cavity, it follows that penicillin should not reach the general circulation from within the cavity. However, the average total urinary excretions in these four patients compare favorably with those obtained following similar administration to normal volunteers.[2] Accurate placement of the penicillin solely at the site of the lesion is not possible. Therefore, the high blood levels and total urinary excretions must be the result of absorption from those portions of the lung that are not diseased. Inasmuch as expectoration was encouraged, a sizeable portion of the administered penicillin was lost in the sputum. Both the blood-level curves and the total urinary excretions are, therefore, somewhat lower with aerosol and intratracheal administration than comparable results obtained with normal lungs.

The demonstrable failure of effectiveness of the parenteral route in the presence of chronic suppuration makes it apparent that direct medication of the lung, either by aerosol or intratracheal instillation, is necessary to alter

favorably the pathologic conditions. The endotracheal method, while simple enough, has several disadvantages. Topical anesthesia is usually employed to assure penetration of penicillin into the distal portions of the tracheobronchial tree. Such suppression of the cough reflex as well as the ever-present risk of reaction to such anesthesia are undesirable. Furthermore, irritation and edema of the vocal cords will occur with repeated manipulation with a catheter.

The chief disadvantage inherent in the aerosol method is the wastage that occurs. We have previously shown that 35 per cent of the aerosolized penicillin actually is absorbed from the lung. From the data presented, however, the marked efficiency of either method in placing many hundred times a minimum therapeutic concentration of penicillin at the site of the disease is apparent. Good levels are maintained for about five hours with intratracheal and for three hours after aerosol administration. A repetition of the aerosol therapy rather than intratracheal injections at these respective time intervals appears to be the more practical method. In fact, it is questionable whether too high concentrations of penicillin are necessary or even desirable in the respiratory tract. Proetz[23] has reported that, while concentrations of 500 units per c.c. of penicillin do not impair the ciliary motion of isolated tracheal strips from the rabbit, concentrations of 5,000 units per c.c. reduce the speed of the ciliary motion within three to six hours, long before signs of surface disintegration occur. Furthermore, Eagle[24] has recently shown that with increasing concentrations of penicillin in body fluids bacteriostasis is not correspondingly increased. On the contrary, after certain optimum concentrations, a paradoxical zone appears and bacteriostasis appears to fall off. It seems, therefore, that more than adequate concentrations of penicillin in purulent lung cavities can be maintained with inhalation of 100,000 units, and possibly smaller doses, every three or four hours. Most patients quickly learn how to use the aerosol apparatus and can, if necessary, continue this form of therapy at home. Proper handbulb aerosolization has been shown to give adequate blood levels.[4] The need for intratracheal manipulation with its attendant disadvantages is, therefore, not present. Although an occasional patient may learn to introduce an intratracheal tube himself,[14] the aerosol method, because of its wide applicability and ease of administration, is to be preferred.

Endotracheal administration may present certain advantages. It is not definitely known how deeply aerosolized penicillin actually penetrates purulent cavities. The addition of wetting agents to the solution may increase the depth of penetration. The only force which carries the minute particles of the aerosol into the lung is the respiratory motion. Drinker and Hardenbergh,[25] during a study of dye and protein absorption from the lung, predicted rapid absorption of as small a molecule as that of penicillin. However, they expressed doubt as to how deeply such inhaled mists would penetrate deep suppurative foci with their lost respiratory motion. May and Floyer[15] felt that aerosols might not enter bronchiectatic cavities any better

than parenteral penicillin because of deficient aeration of the diseased lung. There appears to be little stimulus for minute aerosol particles to enter such a rigid motionless cavity. It appears entirely possible that a thick-walled hollow cavity, unaffected by respiratory motion, could be reached only by a gravitational flow of penicillin such as that which follows direct injection of fluid. Nevertheless, the striking amelioration of symptoms following aerosol therapy, reported by most observers, strongly suggests some penicillin being effective in the depth of such purulent cavities.

Intratracheal therapy, while certainly an effective means of getting the penicillin to where it is most needed, is not recommended for routine use because of previously described disadvantages. However, under certain conditions, it may be the indicated route of therapy: (1) where endotracheal intubation is necessary for other reasons such as at the time of bronchoscopy or bronchography; (2) in thoracic surgery, during routine postoperative tracheal aspirations, to prevent atelectasis and to promote the cough reflex; and (3) where a rapid improvement of symptoms and reduction of sputum are necessary, as for instance, preoperatively to resection for bronchiectasis or abscess. In the last instance, repeated intratracheal administration is certainly less traumatic but probably less effective than repeated preoperative bronchoscopic aspirations with penicillin injection. In all other instances, aerosolization appears to be the ideal method for the medical treatment of such purulent disorders of the lung.

SUMMARY

1. Four patients with chronic purulent disorders of the lung (bronchiectasis and lung abscess) were studied. Each patient received 100,000 units of penicillin intramuscularly, intratracheally, and by the aerosol route. Blood, urine, and sputum specimens were collected over a twenty-four hour period, following administration, and were assayed for their penicillin content.

2. None of the four patients showed detectable penicillin activity in the sputum at any time following intramuscular injection of 100,000 units of penicillin.

3. The blood levels and urine excretion with the endotracheal and aerosol routes were approximately the same as those found in the normal lung. This may be interpreted as demonstrating systemic absorption from the normal portions of the diseased lung.

4. There was expectoration of 14 to 83 per cent of the penicillin administered during the first six hours following intratracheal administration; 5 to 25 per cent of the penicillin was recovered in the sputum following aerosol administration.

5. Both the intratracheal and aerosol methods were shown to be effective. The latter is generally to be preferred except where intubation is necessary for other reasons. The intratracheal route of administration is further suggested as a rapid means of decreasing sputum and cough prior to surgery.

6. Some form of direct medication of the lung is indicated in the treatment of chronic purulent disorders of the lung.

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LIPOID GRANULOMA OF THE LUNG FOLLOWING BRONCHOGRAPHY WITH IODIZED OIL

RICHARD P. STORRS, M.D.,* JOHN R. MCDONALD, M.D.,† AND C. ALLEN GOOD, M.D.‡
ROCHESTER, MINN.

SICARD and Forestier[1] in 1922 in France, using Lipiodol (Lafay), which is iodized poppy-seed oil, introduced iodized oil as a contrast medium for studying the bronchial tree in human subjects. Since then several other oils, including sesame oil, rapeseed oil, olive oil, and peanut oil, have been halogenated with iodine, an iodine-chlorine combination, or bromine and used in bronchography. As a diagnostic measure bronchography has been widely employed and is generally regarded as a relatively safe procedure. There have been reports of acute reactions, a few of them fatal, after bronchography. These have practically all been attributed to anaphylaxis, iodism, or mechanical overfilling or obstruction of bronchi.

We have recently observed a case in which at operation three weeks after bronchography with Iodochlorol (iodized and chlorinated peanut oil) a granulomatous process was found in the lung, apparently caused by the iodized oil. In reviewing the literature we have been able to find reports of only three similar cases in which histologic study of pulmonary tissue showed a pathologic process apparently caused by the presence in the lung of iodized oil.

In 1934, Rabinovitch and Lederer,[2] writing on lipoid pneumonia, stated that one of them had recently observed a case in which post-mortem study revealed changes in the lung similar to those seen in lipoid pneumonia and apparently caused by iodized poppy-seed oil which had been administered sometime before death. They did not give further details of the case.

Wright,[3] in 1935, reported a case of bronchiogenic carcinoma in which, one year after bronchography with iodized rapeseed oil, the opaque medium could be seen roentgenographically in the lung, where it had apparently been trapped by the presence of the tumor in the bronchus. Post-mortem study of the lung in this region showed the presence of much oil in droplets enclosed in a kind of "cellular syncytium," which had replaced nearly all of the pulmonary tissue in the lobe involved. Wright concluded that the reaction had been caused by the prolonged presence of the iodized oil.

In 1943, Brody[4] described a case of what he termed "focal lipid granulomatosis" discovered at operation one month after bronchography had been done using iodized poppy-seed oil. He found in this case, scattered beneath the pleura and throughout the parenchyma of the involved lobes, numerous firm, ovoid, sharply circumscribed, gray-brown nodules, measuring up to 1 cm. in diameter. Microscopically, the nodules consisted of aggregates of tubercle-like structures, the centers of many of which contained fat globules. Many of the fat globules had foreign-body giant cells stretched around them and the latter

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*Fellow in Radiology, Mayo Foundation.
†Section on Surgical Pathology, Mayo Clinic.
‡Section on Roentgenology, Mayo Clinic.

were surrounded by epithelioid cells and macrophages with a peripheral rim of lymphocytes and fibroblasts. Roentgenograms of thin slices of tissue showed radiopaque regions which agreed in size and distribution with the oil droplets seen in the microsections. In this case also a bronchial tumor partially obstructed the bronchi to the lobes in which the granulomatous reaction occurred.

In the case to be reported the findings were very similar to those in Brody's case, except that there was no obstructing bronchial lesion.

REPORT OF CASE

The patient was a white woman, aged 22 years, who registered at the Mayo Clinic in September, 1947. Her history was quite characteristic of bronchiectasis. There was no history of the use of oily nose drops and bronchography had not been done. Stereoscopic roentgenograms of the chest were reported as showing "very extensive bronchiectasis both bases." Bilateral bronchograms using 20 c.c. of Iodochlorol on both sides were done Sept. 25, 1947. Iodochlorol, as described by the manufacturer, contains "27 per cent iodine and 7.5 per cent chlorine in organic combination with a highly refined peanut oil." It is the medium which has been used in bronchography at the clinic almost exclusively for the past six or seven years without ill effect. The bronchograms in this case showed bronchiectasis involving the left lower lobe but because lingular involvement was uncertain, a left bronchogram using 15 c.c. of Iodochlorol was made four days later. This study showed bronchiectasis in the lingula. The patient was hospitalized on Oct. 2, 1947, for preoperative penicillin therapy. Between October 2 and October 5, temperatures of 99.5° F. were recorded on three occasions but during the remainder of the preoperative period her course was afebrile. On October 10 the patient complained of some itching and an erythematous macular type of eruption was noted on the skin of the anterior surface of the chest and thighs, but this apparently subsided rapidly and its nature is uncertain.

On October 14, left thoracotomy was done. At operation the left lower lobe was found to contain many small yellowish gray nodules, some of which lay just beneath the pleura. A similar large region was noted occupying about a third of the volume of the left upper lobe and located chiefly in the anterior basal portion of the lobe. Biopsy of one of the nodules showed lipoid granuloma on fresh frozen section. Left lower lobectomy and lingulectomy were done. When the remaining portion of the left upper lobe was re-expanded it was noted that the nodular region in that lobe was still present.

After operation the patient required oxygen therapy for four days, becoming dyspneic whenever the oxygen was withdrawn. Except for this, her postoperative course was not unusual. Postoperative roentgenograms of the chest showed a large amount of residual iodized oil in both lungs. These roentgenograms showed no shadow which could be said to represent an infiltration in the lung in the vicinity of the solid region described in the left upper lobe at operation, but there was in this region a rather large collection of iodized oil as can be seen on the roentgenogram taken the day after operation (Fig. 1). The remainder of the patient's course was quite satisfactory. When she returned for clinical study, six months later, on April 27, 1948, she reported that she had felt well, had gained weight, and that, although she coughed occasionally, the cough was no longer productive. A roentgenogram of the chest at this time (Fig. 2) showed good expansion of the remaining left upper lobe and a marked reduction of the amount of iodized oil in the lung.

PATHOLOGY

Grossly, the resected portions of the left lung showed bronchiectasis. In addition, the left lower lobe contained a number of solid, yellowish gray areas sharply demarcated from the surrounding lung tissue (Fig. 3). These ranged from 1 mm. to 1.5 cm. in diameter and were grouped in an area involving about

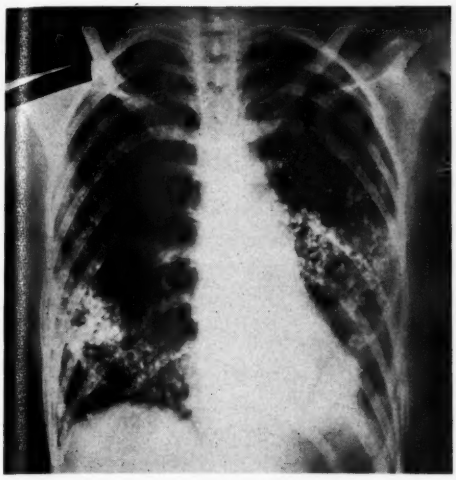


Fig. 1.

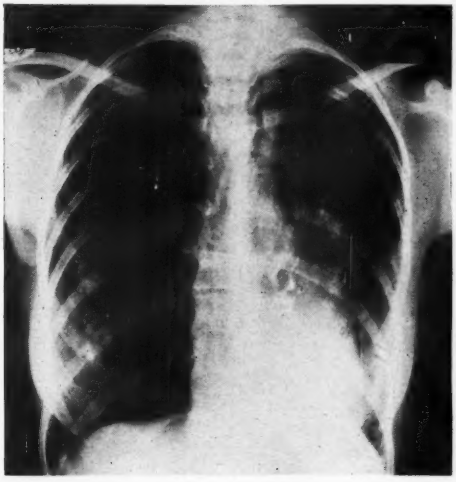


Fig. 2.

Fig. 1.—Roentgenogram of chest taken on day after left lower lobectomy and lingulectomy shows a large amount of residual iodized oil bilaterally. The collection of opaque material in the base of the remaining left upper lobe may represent the solid region described in this lobe at operation.

Fig. 2.—Roentgenogram of chest six months after operation shows good expansion of the remaining left upper lobe and almost complete disappearance of the residual opaque medium seen on the roentgenogram taken immediately after operation.

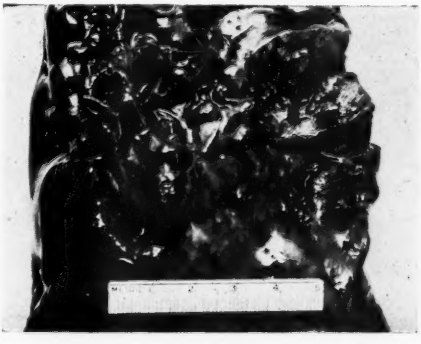


Fig. 3.

Fig. 4.

Fig. 3.—Photograph of the operative specimen (left lower lobe) shows the solid nature of one of the granulomatous nodules where it has been cut across.

Fig. 4.—Roentgenogram of the specimen of the left lower lobe shows that the lung in the solidified region contained a large amount of radiopaque material. The white line represents a wire laid over the specimen to demarcate the region occupied by the nodules as seen grossly.

one-sixth of the left lower lobe in its periphery anteromedially. The larger nodules tended to fuse with one another, forming an irregular region of consolidation with scattered separate nodules around it. A roentgenogram of the specimen showed that the lung in the solidified regions contained a large amount of radiopaque material (Fig. 4). A roentgenogram of a block of tissue from the solid region (Fig. 5) showed the presence of small masses of opaque material, which agreed in size and distribution with small masses of a material which stained orange red with Sudan IV in frozen sections cut from the same block of tissue (Fig. 6).

Fig. 5.

Fig. 6.

Fig. 5.—Roentgenogram of a block of tissue from a region of granuloma shows distribution of opaque medium in this block.

Fig. 6.—Low-power view (×2.7) of a section cut from the block in Fig. 5, stained with Sudan IV, shows small masses of material scattered through the section which appear black in the photograph but were actually bright red.

Microscopic study of tissue from the solid region (Figs. 7 and 8) showed a granulomatous process made up of tubercle-like structures containing various-sized globules of a substance which stained orange red with Sudan IV, blue and crimson with Nile blue sulfate, and black with osmic acid. These staining reactions indicated that the substance in question was an oil. Multinucleated giant cells were found stretched around some of the oil globules. Other oil globules were surrounded by masses of epithelioid cells containing scattered giant cells (Fig. 9). In addition, there were present within the granulomatous tissue regions of definite necrosis in intimate association with masses of oil (Fig. 10). Sections of the surrounding pulmonary tissue which had appeared normal on gross inspection, revealed on microscopic examination a similar but less marked reaction with the presence of mononuclear cells.

Chemical analysis by Dr. M. H. Power showed that tissue from the granulomatous region contained three hundred times as much iodine per gram of wet tissue as did tissue from other regions of the lung which appeared grossly normal.

The gross and microscopic pathologic findings in this case were those of lipoid granuloma. Since the substance found scattered through the granulo-

Fig. 7.

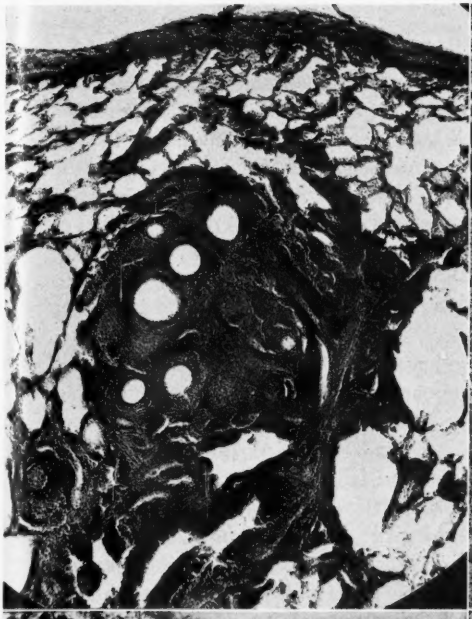
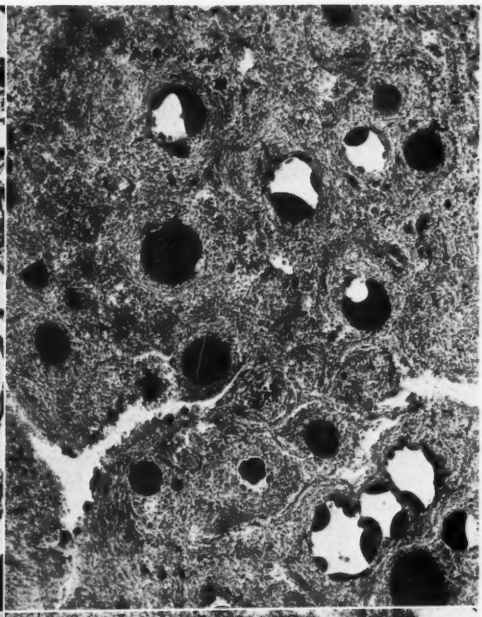


Fig. 8.



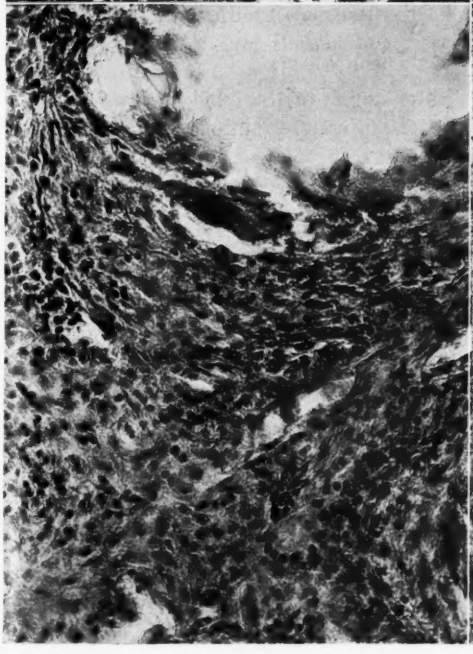


Fig. 9.

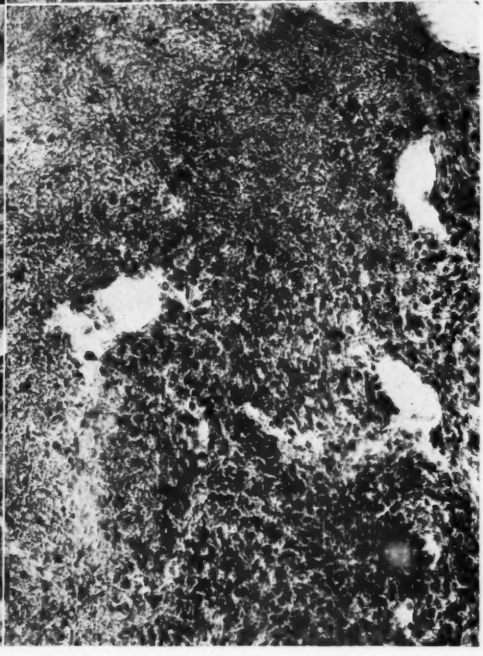


Fig. 10.

Fig. 7.—Low-power view (×26) of one of the smaller nodules stained with hematoxylin and eosin. The nodule is sharply circumscribed from the surrounding lung tissue and has at its center clefts which contained iodized oil. The oil has been dissolved out in tissue processing.

Fig. 8.—Section stained with Sudan IV shows solid region of granuloma containing small masses of oil which stained bright red but which appear black in the photograph (×55).

Fig. 9.—Higher power view (×110) of section stained with hematoxylin and eosin shows epithelioid cells and a giant cell adjacent to a cleft which once contained an oil droplet.

Fig. 10.—Granuloma with an area of necrosis in the upper left-hand corner (hematoxylin and eosin ×90).

matous regions and at the centers of the granulomatous nodules was by staining reaction an oil, by roentgenographic examination an opaque substance, and by chemical analysis of high iodine content, the conclusion that it was the iodized oil used for bronchography seems certain. The relation of the oil globules to the granuloma is such that one must conclude that the granuloma developed in response to the presence of the iodized oil.

COMMENT

The question of what reaction might be caused in the lung by the introduction of iodized oils used in bronchography has stimulated considerable investigation. Ballon and Ballon,[5] in 1927, from a study of 100 cases in which Lipiodol bronchography had been done and from experimental work with cats, concluded that there was no immediate reaction to this substance and no late reaction when it persisted in the lung even for long periods. Fried and Whitaker,[6] in the same year, using iodized poppy-seed oil and iodized sesame oil, studied the histologic change in the lungs of animals at intervals after intratracheal injection. They reported that the reaction to the oil in the lungs was confined to the cells lining the alveolar walls, which, being normally macrophages in a resting state, became transformed into wandering phagocytes and picked up the oil in their cytoplasm. They found regions where these cells proliferated, forming cellular, tumorlike masses which collapsed the alveoli and destroyed the normal architecture of the lungs.

In 1928, Pinkerton[7] made studies of the reaction of the lungs of dogs and rabbits to various oils with particular interest in determining whether the iodized oils used in bronchography were capable of producing reactions similar to those known to have been produced by other oils. He concluded: (1) that most vegetable oils (including iodized poppy-seed oil and iodized sesame oil) produced practically no reaction in the lungs even though retained there for a considerable period; (2) that mineral oil was quickly emulsified in the lungs and taken up by phagocytes which collected in large numbers, filling the alveoli and producing consolidation, which was later followed by fibrosis; (3) that animal oils (such as lard oil and cod liver oil) produced solid yellowish regions in the lung which microscopically showed masses of oil surrounded by a tubercle-like granulomatous reaction made up of giant cells and mononuclear phagocytes with occasional regions of necrosis, particularly when animal oils containing a relatively high percentage of fatty acids had been used; (4) that the reaction of the lungs to an oil varied directly with the free fatty acid content of that oil; and (5) that the simple vegetable oils used in bronchography, since they had a very low content of free fatty acid and apparently were little affected by the lipase activity of the lungs to be broken down to fatty acids, were quite safe for use.

Brown,[8] in 1928, studied the reaction of the lungs of cats to injections of iodized oil and concluded that the presence of the oil in healthy alveoli excited a mononuclear infiltration of the large phagocytic type and that these large phagocytes were the prime factors in the removal of the oil from the alveoli, carrying the oil along the lymphatics to the hilar lymph nodes.

In 1929, Bettman, Kelly, and Crohn,[9] using dogs, reported that most of the iodized poppy-seed oil introduced intratracheally was expelled from the bronchial tree by coughing and that even though small amounts were retained for as long as seven months, the presence of this oil did not cause a definite foreign-body reaction.

Bezançon, Delarue, and Valet-Bellot,[10] in France, in 1935, reported histologic studies of post-mortem material from three cases observed two days, twelve days, and six years after instillation of iodized oil. They concluded that: (1) iodized oil used in bronchography reached the alveoli, where the greater part of it remained free, not causing any histologic reaction and being removed by expectoration; (2) a small part of the oil was rapidly fixed in the alveolar walls by a process of intraparietal phagocytosis, producing a mild interstitial reaction and being gradually broken down by the lipolytic action of the pulmonary parenchyma. They suggested that the long retention of iodized oil occasionally observed on roentgenograms was due to a deficiency of the lipolytic activity of the lungs.

Gowar and Gilmour,[11] in 1941, reported on histologic studies of the lungs of rabbits at intervals after injection of an iodized oil and concluded that the only pathologic change that could definitely be attributed to the iodized oil was the presence of epithelioid cells which formed nodules. They found little evidence of phagocytosis of the oil and no evidence of removal of the oil from the lung by migration of macrophages. Chesterman,[12] in 1942, using essentially the same technique with cats, found that three of eleven animals into which iodized oil had been injected showed sharply circumscribed regions of consolidation which were grossly yellow and which microscopically showed large phagocytic cells containing globules of oil, together with exudation of polymorphonuclear leucocytes and epithelial proliferation.

The pathologic evidence in this case, in our opinion, indicates definitely that the granulomatous process found in the lung at operation was caused by the presence of the iodized peanut oil introduced for the purpose of making bronchograms. The recognition of such a process developing in response to iodized oil must be a very rare occurrence, since so few similar cases have been reported. It seems entirely possible, however, that lesser degrees of such reaction may occur more often than has been recognized. Studies with animals, using various iodized oils, have indicated that there is usually little reaction of the lung to these substances, but investigators have reported finding masses of epithelioid cells which had destroyed the normal pulmonary architecture in some regions. These masses of epithelioid cells were apparently quite small in most instances but could represent a mild degree of the same reaction as was present in this case.

It seems very unlikely that the iodized peanut oil used in this case was any different from that which has been used in hundreds of other cases here and one must conclude that the pulmonary tissue of this patient reacted in a different manner to contact with iodized peanut oil than does the pulmonary tissue of the average person. The reaction found in this lung with formation of granuloma and necrosis was very similar to that which Pinkerton described

as occurring in response to animal oils of high fatty acid content. Perhaps this patient's lung possessed a very high degree of the lipase activity, described by several French writers, and rapidly broke down a portion of the peanut oil, releasing irritating fatty acids which caused the necrosis and the formation of granuloma.

The question whether peanut oil might be undesirable as a base for iodized oil has been considered. Boldrey and Aird,[13] in 1944, after experimental studies concluded that iodized peanut oil injected intrathecally was less irritating to the meninges than iodized poppy-seed oil. Since peanut oil has been used at the clinic in bronchography for such a long period with only one proved reaction of this type, and since the only similar reactions reported in the literature occurred after the use of other oils, one must conclude tentatively at least that peanut oil is probably as good a base as the other oils currently in use.

The clinical importance of the reaction in this case was an apparent reduction of the patient's pulmonary reserve, requiring the use of oxygen therapy for a comparatively long period after operation. The process, as far as can be determined clinically, was a reversible one and the outcome was satisfactory. It would seem, in view of the reaction in this case, most desirable to empty the bronchial tree of iodized oil as quickly and completely as possible after bronchography. In addition, it would seem advisable to make roentgenograms of the chest prior to surgical intervention in all cases in which bronchography has been performed and to delay surgical intervention in those cases in which any considerable amount of residual iodized oil is observed in the roentgenograms.

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THE EFFECT OF PNEUMONECTOMY ON PULMONARY FUNCTION

W. Emory Burnett, M.D., Joan H. Long, M.D., Charles Norris, M.D.,
George P. Rosemond, M.D., and Mary R. Wester, M.S.
Philadelphia, Pa.

DESPITE the fact that pneumonectomy has been an accepted surgical procedure since 1933,[1] there have not been many reports on the changes in pulmonary function with pneumonectomy.[2-6] Often these reports have consisted only of the measurement of the function postoperatively and an estimation of "normal" function preoperatively. In the present study measurements of pulmonary function were made both pre- and postoperatively by means of external spirometry and bronchospirometry.

These studies of pulmonary function before and after pneumonectomy were done on patients at Temple University Hospital. External spirometry measuring the over-all function of both lungs was carried out on twenty-four patients. An evaluation of the ventilatory function at rest and during a period of voluntary maximum effort was made. In sixteen patients the division of function between the right and left lungs was determined prior to operation by means of bronchospirometry. This was done in order to estimate the functional impairment of the lung to be resected as well as to bring out possible undetected impairment of function of the contralateral lung. Pneumonectomy was performed in twenty-one instances for pulmonary neoplasm, and in the remaining three for extensive unilateral bronchiectasis. The patients ranged in age from 35 to 66 years, the average age being 53 years. There were seventeen men and seven women.

External spirometry was carried out with the patients in a basal condition, using a Roth-Benedict water spirometer. A record of quiet respiration was obtained over a period of 5 to 6 minutes; the spirogram thus obtained was used for analysis of the oxygen absorbed per minute, the respiratory rate, the depth of respiration (tidal air), and the average minute volume of respiration (M.V.R.), that is, the respiratory rate times the tidal air. The maximum breathing capacity was recorded after asking the patient to breathe as deep and as fast as possible, as though he had been running. The record was continued for a period of one-half minute during which time the patient was frequently encouraged to breathe deeper and faster. For the short period of recording the maximum breathing capacity and recovery the soda lime container was removed from the spirometer to eliminate the resistance of the lime itself and the resistance of one flutter valve. The maximum breathing capacity (M.B.C.) was calculated in terms of liters per minute. The breathing reserve at rest was derived. (M.B.C. – M.V.R.). The per cent breathing reserve was also calculated according to the formula

$$\frac{\text{M.B.C.} - \text{M.V.R.}}{\text{M.B.C.}} \times 100.$$

From the Departments of Surgery, Bronchoesophagology, and Physiology, Temple University Medical School and Hospital.
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Repeated determination of resting minute volume and maximum breathing capacity by this method on the same day, successive days, or within a few weeks showed remarkable constancy of ventilatory function, particularly with regard to the depth of respiration both during quiet breathing and during maximum effort.* It was, therefore, felt that it was valid to compare the results obtained by this method before and after pneumonectomy. These results cannot be compared with those obtained on the Douglas bag by other investigators, since the depth of respiration both during quiet breathing and during maximum effort appear to be greater on the spirometer, probably due to the greater resistance of the closed circuit.

External spirometry was done before and after pneumonectomy in all twenty-four cases. The postoperative studies were carried out two to three weeks after pneumonectomy in sixteen cases, and two months to two years later in nineteen cases.

Bronchospirometry was performed preoperatively on sixteen patients. A Gebauer twin spirometer was used. Originally a Zavod catheter was used; later a Norris catheter[7] was substituted for the Zavod, as we felt it gave more accurate results. The patients were not in a basal condition. Under local Pontocaine anesthesia and using fluoroscopic guidance the catheter was put in place with the tip in the left main bronchus. The procedure has been more fully described elsewhere.[7]

The division of function between the two lungs was calculated from the bronchospirometric record. This included the per cent of the total oxygen absorbed from the right and left lungs, respectively, and the per cent of the total volume of air moved by each lung. By referring these relative functions of each lung back to the resting oxygen absorption and tidal volume as determined by external spirometry under basal conditions, the probable resting function of each lung was estimated. The maximum breathing capacity of each lung was calculated from the percentage of the total tidal air moved by each lung and the total maximum breathing capacity as obtained by external spirometry. Such an estimation of the maximum breathing capacity of the separate lungs is valid only if the proportion of air ventilated by each lung is the same with a maximum ventilatory effort as during rest. Recent work has shown that this is not always so. For instance, in unilateral emphysema there may be a difference between the percentage of air ventilated by the involved lung during quiet respiration and during great respiratory effort.[8] It would seem, then, that our estimated figures for the maximum breathing capacity of the separate lungs preoperatively may be open to some question, but at the moment they are the best available.

*A total of 130 tests were done on 45 individuals at intervals ranging from one-half hour to several months. The average variation in resting minute volume was 1.2 L., in maximum breathing capacity 7 per cent; the average variation in the depth of respiration during quiet breathing was 85 c.c. and during maximum effort 196 c.c. Using the figures obtained it was found that differences of less than 2.5 L. in resting minute volume, and of less than 15 per cent in maximum breathing capacity were insignificant. Likewise, a change of less than 200 c.c. in resting tidal volume or of 300 c.c. in the depth of respiration obtained during maximum effort was insignificant.

RESULTS

The results may be considered in two categories: the changes in the total pulmonary function after pneumonectomy and the changes in the function of the remaining lung (Tables I and II).

The changes in total function are shown in Table II. Seventeen patients were examined two to three weeks after pneumonectomy. In general, the respiration tended to be more rapid and somewhat less deep in the immediate postoperative period than prior to operation, but in only five instances was the respiratory rate above 20. In two cases of pulmonary suppuration prior to operation the respiratory rate dropped below 20 after removal of the diseased lung. Twenty patients were re-examined two to twenty-four months postoperatively. All except three had respiratory rates below 20. In almost all the patients who were studied both immediately postoperatively and then some months later the respiratory rates had decreased below the two weeks postoperative rate, although they were in some instances still slightly higher than the preoperative rates. The depth of respiration was often less postoperatively than it had been preoperatively. There was usually no significant change in the minute volume of respiration.

Preoperatively, the maximum breathing capacities ranged from 17.1 L. to 60.8 L. per minute. These values are far below the expected normals as estimated by Cournand.[5]* The resting breathing reserves (M.B.C. – M.V.R.) ranged from 9.9 to 52.7 L. The percentage breathing reserves ($\frac{\text{M.B.C.} - \text{M.V.R.}}{\text{M.B.C.}} \times 100$) preoperatively ranged from 42 to 88 per cent. Postoperatively the maximum breathing capacity usually decreased; there was a decrease in the depth of respiration during maximum ventilatory effort in all but one case (Case 10) and usually an increase in rate. In a few cases the increased rate compensated for the decreased depth so well that the maximum breathing capacity postoperatively actually closely approached or even exceeded the preoperative determination.

Changes in resting breathing reserve usually paralleled the changes in the maximum breathing capacity. Interestingly enough, after the immediate postoperative period there were eight patients in whom there was an increase and two patients in whom there was less than a 2 L. decrease in the breathing reserve after the removal of one lung. In the remaining nine patients the decrease in reserve ranged from 5 to 31 L.

Except, then, for the decrease in maximum breathing capacity (average decrease 23 per cent), the changes in the over-all resting pulmonary function picture with pneumonectomy were not great. However, the changes in the function of the remaining lung were often striking and indicative of compensatory adjustments to maintain the resting pulmonary function at its preoperative level.

With the patient in a basal condition the oxygen absorption of the remaining lung increased an average of 80 per cent. If the basal oxygen of the in-

*For men: estimated normal M.B.C. (86.5—[0.522 × age]) × surface area in meters.^{2}
For women: estimated normal M.B.C. (71.3—[0.474 × age]) × surface area in meters.^{2}

TABLE I. RESULTS OF PULMONARY FUNCTION TESTS BEFORE AND AFTER PNEUMONECTOMY*

CASE NO.	SEX	AGE	TIME	O_2 USE (C.C./MIN.) TOTAL	RIGHT	LEFT	RATE	TIDAL VOLUME (C.C.) TOTAL	RIGHT	LEFT	M.V.R. LITERS	M.B.C. LITERS	B.R. LITERS	B.R. PER CENT	LESION AND OPERATION
1	F	57	Preop.	217	102	115	17	500	250	250	8.5	26.0	17.5	67	Carcinoma left lung
					47%	53%			50%	50%					Left pneumonectomy
			16 mo.		275		17		350		6.0	18.2	12.2	64	
2	M	63	Preop.	300	132	168	16	400	208	192	6.4	30.8	24.4	79	Carcinoma right lung
					44%	56%			52%	48%					Right pneumonectomy
			12 mo.			300	15			550	8.2	31.6	23.4	74	
			24 mo.			273	21			550	11.5	52.5	41.0	78	
3	M	47	Preop.	316	123	193	16	500	230	270	8.0	24.0	16.0	67	Carcinoma right lung
					39%	61%			46%	54%					Right pneumonectomy
															Empyema postop.
			3 wk.			315	17			550	9.4	16.2	6.8	42	
			3 mo.			237	15			500	7.5	18.0	10.5	58	
			12 mo.			253	16			450	7.2	22.0	14.8	67	
4	M	51	Preop.	188	123	65	6	1300	718	582	7.8	19.0	11.2	59	Carcinoma right lung
					65%	35%			55%	45%					Right pneumonectomy
															Empyema postop.
			4 mo.			320	15			500	7.5	16.0	8.5	53	Right thoracoplasty
			7 mo.			250	13			450	5.9	15.2	9.3	61	
			12 mo.			210	12			650	7.8	28.0	20.2	72	
5	F	37	Preop.	200	116	84	12	700	380	320	8.4	20.3	11.9	59	Carcinoma right lung
					58%	42%			55%	45%					Right pneumonectomy
			22 mo.			206	12			450	5.4	15.4	10.0	65	
6	M	58	Preop.	250	162	88	8	1000	750	250	8.0	57.0	49.0	86	Carcinoma left lung
					65%	35%			75%	25%					Left pneumonectomy
															Empyema postop.
			3 wk.		220		6		900		5.4	42.5	37.1	87	
			5 mo.		250		9		800		7.2	43.7	36.5	83	
7	M	42	Preop.	183	121	62	7	1150	830	320	8.1	60.8	52.7	87	Carcinoma left lung
					66%	34%			72%	28%					Left pneumonectomy
															Spread to mediastinum
			2 wk.		240		18		450		8.1	38.0	29.9	79	
			6 mo.		266		17		600		10.2	30.0	19.8	66	
8	F	42	Preop.	266	144	122	17	300	75	225	5.1	38.4	33.3	87	Carcinoma right lung
					54%	46%			25%	75%					Right pneumonectomy
			2 wk.			186	25			250	6.3	19.5	13.2	68	
			3 mo.			150	17			300	5.1	9.5	4.4	46	
			4 mo.			283	18			290	5.2	25.2	20.0	79	
			6 mo.			166	16			350	5.6	24.0	18.4	77	

9	F	47	Preop.	200	62 31%	138 69%	11	625	305 49%	320 51%	6.9	17.1	10.2	60	Carcinoma right lung Right pneumonectomy
			2 wk.			216	17			650	11.1	16.2	5.1	31	
			22 mo.			140	10			475	4.8	15.4	10.6	70	
			30 mo.			200	12			470	5.6	21.6	16.0	74	
10	F	41	Preop.	238	238 100%	--- 0%	24	400	400 100%	--- 0%	9.6	21.7	12.1	56	Far advanced bronchiectasis Left pneumonectomy
			2 wk.		226		10		650		6.5	23.4	16.9	72	
			5 mo.		150		20		850		17.0	33.3	16.3	67	
			18 mo.		250		21		600		12.6	29.4	16.8	57	
11	F	58	Preop.	288	259 90%	28 10%	13	700	490 70%	210 30%	9.1	29.4	20.3	71	Carcinoma left lung Far advanced tuberculosis left Left pneumonectomy
			7 mo.		233		12		700		8.4	22.5	14.1	63	
12	M	56	Preop.	300	212 74%	88 26%	23	450	324 71%	126 29%	10.4	36.8	26.4	72	Carcinoma left lung Left pneumonectomy
			2 wk.		217		24		400		9.6	32.4	22.8	70	
13	M	47	Preop.	200	88 44%	112 56%	10	1300	663 51%	637 49%	13.0	50.4	37.4	74	Carcinoma right lung Right pneumonectomy
			2 wk.			287	18			450	8.1	27.0	18.9	70	
14	M	44	Preop.	226	146 69%	80 31%	12	650	400 61%	250 39%	7.8	52.8	45.0	85	Carcinoma left lung Left pneumonectomy
			2 wk.		233		15		500		7.5	22.0	14.5	66	
15	M	35	Preop.	325			18	750			13.5	32.3	18.8	58	Advanced bronchiectasis Left pneumonectomy
			2 wk.		300		27		500		13.5	17.0	3.5	21	
			3 mo.		225		25		625		15.6	24.6	9.0	37	
			10 mo.		400		23		650		14.9	41.4	26.5	64	
16	M	61	Preop.	200			17	500			8.5	39.6	31.1	79	Carcinoma right lung Right pneumonectomy
			1 yr.			150	20			550	11.0	25.2	14.2	56	
17	M	60	Preop.	350			11	500			5.5	18.0	12.5	70	Carcinoma left lung Left pneumonectomy
			2 wk.		265		26		380		9.9	21.0	11.1	57	
			6 mo.		340		14		600		8.4	18.2	9.8	54	
			18 mo.		233		16		600		9.6	22.8	13.2	58	
18	F	52	Preop.	215			12	540			6.5	54.0	47.5	88	Carcinoma right lung Right pneumonectomy
			7 mo.			175	18			400	7.2	30.0	22.8	76	

*The oxygen use and tidal volume given for the right and left lungs preoperatively are based on the per cent division of function as determined by bronchospirometry.

M.V.R.—minute volume of respiration.

M.B.C.—maximum breathing capacity.

B.R. —breathing reserve (M.B.C.—M.V.R.).

$$\% \text{ B.R.} = \frac{\text{M.B.C.} - \text{M.V.R.}}{\text{M.B.C.}} \times 100$$

(Table I continued on following page)

TABLE I—CONT'D

CASE NO.	SEX	AGE	TIME	O_2 USE (C.C./MIN.) TOTAL	RIGHT	LEFT	RATE	TIDAL VOLUME (C.C.) TOTAL	RIGHT	LEFT	M.V.R. LITERS	M.B.C. LITERS	B.R. LITERS	B.R. PER CENT	LESION AND OPERATION
19	M	62	Preop.	216			29	500			14.5	25.0	10.5	42	Carcinoma left lung Left pneumonectomy
			2 wk.		160		19		425		8.2	11.4	3.2	28	
20	M	40	Preop.	280			14	550			7.7	41.8	34.1	82	Advanced bronchiectasis Left pneumonectomy
			6 mo.		312		11		550		6.1	29.7	23.6	79	
21	M	52	Preop.	300			17	450			7.7	17.6	9.9	56	Carcinoma right lung Right pneumonectomy
			2 wk.			330	20			400	8.0	12.0	4.0	33	
			3 mo.			250	15			450	6.8	16.5	9.7	58	
			6 mo.			240	17			450	7.6	18.2	10.6	58	
22	M	66	Preop.	180			10	800			8.0	55.2	47.2	86	Carcinoma right lung Right pneumonectomy
			12 days			233	14			500	7.0	27.0	20.0	74	
23	M	57	Preop.	276	210 75%	66 25%	18	550	430 78%	120 22%	9.9	39.0	29.1	75	Carcinoma left lung Left pneumonectomy
			2 wk.		350		25		400		10.0				
			3 mo.		250		21		350		7.4	40.0	32.6	82	
24	M	64	Preop.	243	110 47%	132 53%	12	900	530 59%	370 41%	10.8	56.0	45.2	81	Lymphosarcoma Left pneumonectomy
			2 wk.		276		16		700		11.2	27.3	16.1	59	
			2 mo.		333		14		750		10.5	32.6	22.1	68	

dividual were to remain constant, it would obviously follow that the remaining lung would increase its absorption of oxygen to the extent necessary to provide the amount formerly absorbed from the diseased lung. Theoretically, if half of the total oxygen were provided by each lung preoperatively, then postoperatively the remaining lung must necessarily double its oxygen uptake. Considering only those patients (Cases 2, 5, 6, 8, 9, 10, and 14) in whom the over-all oxygen absorption was approximately the same before and after operation, it may be seen that the increase in oxygen absorption from the remaining lung is inversely proportional to the per cent of the total oxygen provided by that lung preoperatively. For example (Case 2) when the remaining lung preoperatively was absorbing 56 per cent of the total oxygen, postoperatively its oxygen absorption was not quite doubled (1.8 times); when the oxygen absorption preoperatively was 46 per cent of the total oxygen (Case 8), the oxygen uptake by the remaining lung was a little more than doubled (2.3 times) postoperatively. When the oxygen consumption was increased greatly because of infection (Case 4), the increase in oxygen uptake from the remaining lung was almost five times the preoperative value.

The minute volume changes were not proportional to the changes in oxygen absorption; the oxygen absorption of the remaining lung increased more than did the minute volume. On an average, preoperatively, the uninvolved lung absorbed 100 c.c. of oxygen for every 3.7 L. of air moved; two weeks postoperatively it absorbed 100 c.c. of oxygen for every 3.4 L. of air moved, and several months postoperatively, 100 c.c. of oxygen for every 2.6 L. of air moved.

The depth of respiration (tidal volume) of the remaining lung increased except in one instance. During the immediate postoperative period the average increase in depth was 51 per cent and after several months the average increase in depth was 70 per cent. In one case the depth of respiration increased by 112 per cent. These changes in depth coupled with the usual increase in the rate of respiration produced an average increase in the minute volume of the remaining lung of 55 per cent.

The maximum breathing capacity *of the remaining lung* tended to increase postoperatively due in the main to an increase in the rate of respiration during maximum voluntary effort. Using the calculated preoperative values the increase in the depth of respiration of the remaining lung during maximum effort apparently amounted to no more than 300 c.c. with one exception when there was an increase of 570 c.c. In two patients the M.B.C. of the remaining lung decreased postoperatively. One patient had developed hemiplegia with marked muscular weakness, so that the rate of respiration during maximum effort was greatly decreased. The second patient had had extension of the bronchial carcinoma to the mediastinum and had received x-ray therapy over the mediastinal area. In this case there was a 56 per cent decrease in the depth of respiration during maximum effort.

DISCUSSION

Pneumonectomy in patients with little or no disease in the contralateral lung caused remarkably little change in resting oxygen absorption or the minute

TABLE II. COMPARISON OF THE MAXIMUM BREATHING CAPACITY

CASE NO.	TIME	MAXIMUM BREATHING CAPACITY					BREATHING RESERVE LITERS	BREATHING RESERVE PER CENT	MEDIASTINAL SHIFT*	DYSPNEA
		TOTAL LITERS	RATE	DEPTH C.C.	RIGHT C.C.	LEFT C.C.				
1	Preop.	26.0	20	1300	650	650	17.5	67	–	None
	16 mo.	18.2	26		700		12.2	64	–	None on 1 flight of stairs
2	Preop.	30.0	22	1400	720	680	24.4	79	–	On moderate exertion
	24 mo.	52.5	42			1250	41.0	78	+++	None on 1 flight of stairs Working in store 12-14 hrs. a day
3	Preop.	24.0	16	1500	690	810	16.0	67		On slight exertion
	22 mo.	22.0	22			1000	14.8	67	0	On hurrying up stairs Working as garage mechanic
4	Preop.	19.0	10	1900	1050	850	11.2	59		On walking
	12 mo.	28.0	28			1000	20.2	72	0	On walking
5	Preop.	20.3	14	1450	800	650	11.9	59		Difficult to evaluate ''attacks'' of dyspnea
	22 mo.	15.4	22			700	10.0	65	+++	On exertion
6	Preop.	57.0	30	1900	1450	470	49.0	86		On stairs
	5 mo.	43.7	38		1150		36.5	83	0	On stairs
7	Preop.	60.8	32	1900	1370	530	52.7	87		None
	6 mo.	30.0	50		600		19.8	66	–	At rest
8	Preop.	38.4	48	800	200	600	33.3	87		None
	6 mo.	24.0	32			750	18.4	77	+++	On stairs
9	Preop.	17.1	18	950	550	400	10.2	60		On exertion
	22 mo.	21.6	24			900	16.0	74	+++	Works 8 hr. day as a waitress; dyspnea only on 2 flights of stairs
10	Preop.	21.7	28	775	775	0	12.1	56		?
	18 mo.	29.4	28		1050		16.8	74	+++	None on stairs; does housework
11	Preop.	29.4	28	1050	730	320	20.3	71		None
	7 mo.	22.5	30		750		14.1	63	++	None on stairs
23	Preop.	39.0	26	1500	1170	330	29.1	75		On exertion
	3 mo.	40.0	40		1000		32.6	82	+	On stairs
24	Preop.	56.0	28	2000	1180	820	45.2	81		None
	2 mo.	32.6	46		710		22.1	68	+	On exertion; readily fatigued
15	Preop.	32.3	38	850			18.8	58		On walking
	10 mo.	41.4	46		900		26.5	64	+	None on walking but on 1 flight of stairs
16	Preop.	39.6	36	1100			31.1	79		On stairs
	12 mo.	25.2	28			900	14.2	56	+++	On stairs; unable to work
17	Preop.	18.0	20	900			12.5	70		On stairs
	18 mo.	22.8	38		600		13.2	58		On walking
18	Preop.	54.0	36	1500			47.5	88		None
	7 mo.	30.0	30			1000	22.8	76		None
20	Preop.	41.8	22	1900			34.1	82		On exertion
	6 mo.	29.7	22		1350		23.6	79	+	On exertion; does light work

TABLE II—CONT'D

CASE NO.	TIME	MAXIMUM BREATHING CAPACITY					BREATHING RESERVE LITERS	BREATHING RESERVE PER CENT	MEDIASTINAL SHIFT*	DYSPNEA
		TOTAL LITERS	RATE	DEPTH C.C.	RIGHT C.C.	LEFT C.C.				
21	Preop.	17.6	16	1100			9.9	56		On exertion
	6 mo.	18.2	26			700	10.6	58	++	None on 1 flight of stairs
12	Preop.	36.8	32	1150	820	330	26.4	72		None
	2 wk.	32.4	36		900		22.8	70	0	-
13	Preop.	50.4	18	2800	1430	1370	37.4	74		None
	2 wk.	27.0	30			900	18.9	70	++	-
14	Preop.	52.8	22	2400	1460	940	45.0	85		On exertion
	2 wk.	22.0	22		1000		14.5	66	+	-
19	Preop.	25.0	26	960			10.5	42		On walking
	2 wk.	11.4	19		600		3.2	28	+	At rest
22	Preop.	55.2	20	1500			47.2	86		None
	2 wk.	27.0	36			750	20.0	74		-

*As shown by roentgen examination.

volume of ventilated air. This lack of change resulted from adjustments of the remaining lung to the altered situation.

Absorption of oxygen from the one remaining lung increased sufficiently to meet the resting needs of the individual. Since oxygen absorption by the blood is a physicochemical process, the increase in oxygen absorption by the remaining lung of 80 per cent or more suggests that there has been an increase in the volume of blood flowing through that lung per minute. Such an increase in volume could be accomplished in two ways, by an increase in the rate of blood flow or by an increase in the functioning capillary bed of the remaining lung. The latter is the explanation which has been advanced at separate times by Tigerstedt,[9] Wiggers,[10] and Cournand.[5]

If the total capillary bed of the remaining lung does not change, and the functioning capillary bed increases as is suggested by the oxygen absorption, then the reserve or nonfunctioning capillary bed of that lung is decreased. One could postulate that the reserve capillary bed might no longer be as adequate to meet an increased cardiac output or an increase in blood volume as was the entire capillary bed of both lungs preoperatively. That the reserve of the remaining lung is not always adequate is suggested by the fact that 20 per cent of these patients with apparently normal hearts developed pulmonary edema with the increased stress of the first few postoperative days. However, recovery followed treatment and there has been no further evidence of pulmonary edema or heart failure in this group of patients.

The total volume of air ventilated per minute was changed insignificantly by pneumonectomy. This constancy of the over-all picture was maintained by means of a slightly more rapid rate of respiration coupled with an increased volume of air taken in at each breath by the remaining lung. The increase in the tidal volume of the uninvolved lung amounted to more than 100 per cent in a few instances.

On the whole, one was unable to predict too accurately from the maximum breathing capacity or the per cent breathing reserve what the patient's symp-

toms with regard to dyspnea were. Preoperatively there were two patients with breathing reserves of 85 per cent and 86 per cent who had dyspnea on moderate exertion. On the other hand, there was one patient with a breathing reserve as low as 67 per cent (17 L.) with no dyspnea.

All of the patients, three with breathing reserves below 11 L., successfully tolerated the operative procedure. There was no correlation between the preoperative breathing reserves and postoperative pulmonary edema when it occurred.

Pneumonectomy did not necessarily change the amount of dyspnea experienced by the patient during ordinary activity (not exercise). Five of the patients whose postoperative reserves ranged from 61 per cent to 70 per cent and whose x-ray films showed overdistention of the remaining lung, had no dyspnea except when hurrying against a cold wind. They did, of course, have a decreased exercise tolerance, but their normal activities did not often cause them to exceed it. Eleven patients who had been dyspneic on exertion preoperatively still had the same amount of dyspnea postoperatively. Their reserves ranged from 83 per cent to 56 per cent. They carried on their normal activities but performed tasks more slowly. An interesting observation on these patients was that although they did not complain of dyspnea they often had a noticeable increase in the rate of respiration when walking at a normal pace. One wonders if a patient with a pneumonectomy responds to increased oxygen need by an increase in respiratory rate rather than by an increase in the depth of respiration. One activity which seemed to cause definite dyspnea was the act of bending over. Such an act limits the motion of the diaphragm.

There were three patients in whom there was an improvement of effort capacity postoperatively. These individuals had had bronchiectasis, and they gained in weight and strength after the removal of the chronically infected lung. In only four patients was there any marked increase in dyspneic symptoms after pneumonectomy and each of these patients had other factors in addition to the pneumonectomy which impaired the respiratory function, such as hemiplegia with partial paralysis of the muscles of respiration, extension of the carcinoma into the mediastinum and into the other lung, or severe infection.

In summary, we have found that there may be remarkably little change in the over-all measurement of resting pulmonary function as a result of pneumonectomy. However, rather large compensatory changes do occur in the remaining lung; the resting depth of respiration may be as much as doubled, the minute volume may be tripled, and the oxygen absorption may be more than doubled to meet the resting oxygen demands of the individual. This means that the one remaining lung can successfully compensate for the loss of functioning lung tissue caused by pneumonectomy in most instances with but little increase in respiratory rate when the patient is at rest.

This does not mean that pulmonary function is within normal limits; in most of our patients it was definitely below normal, but it had also been below normal prior to operation. In most of the patients there was a lessened ability

to increase the ventilation of the lungs upon demand, i.e., a decrease in the breathing reserve. In fact, what increase in ventilation there was on effort depended much more upon an increase in the rate of respiration than it had prior to pneumonectomy. However, the decreases in breathing reserve were associated with subjective dyspnea only if the individual was required to undertake some activity requiring considerable muscular effort, and since most patients undergoing pneumonectomy were in the older age group, it was not often that their normal activities were strenuous enough to cause this. The cases which showed considerable functional impairment after pneumonectomy usually had other factors complicating the postoperative course such as hemiplegia or spreading carcinoma.

SUMMARY

1. Pulmonary function studies have been compared before and after pneumonectomy in twenty-four patients.

2. Pneumonectomy produced little or no change in the over-all resting tidal volume, minute volume, and oxygen consumption of these patients.

3. Pneumonectomy usually reduced the maximum breathing capacity and the breathing reserve by reducing the depth of respiration during maximum respiratory effort.

4. This lack of change in over-all resting pulmonary function after pneumonectomy was due to compensatory adjustments of the remaining lung, namely: (a) an increase in tidal volume, (b) an increase in minute volume, and (c) an increase in the oxygen uptake.

5. There was little or no increase in the depth of respiration of the remaining lung during maximum respiratory effort. What increase occurred in the maximum breathing capacity of the remaining lung was due to an increase in the rate of respiration.

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LACTATION FOLLOWING THORACOPLASTY AND PNEUMONECTOMY

DAVID SALKIN, M.D.,* HOPEMONT, W. VA., AND EDGAR W. DAVIS, M.D., WASHINGTON, D. C.

NONPUERPERAL lactation has been described frequently.[1, 2, 3] In the commoner instances it may occur for some months or years following weaning, at the time of the menopause, in cystic disease of the breast, in cases of ovarian tumors, and following removal of the ovaries. In the rarer cases it has been described following titillation and suckling of the breast in virgins, after a severe burn of the breast, in carcinoma of the pituitary gland, and at the time of menstruation. It has been described as occurring even in men with disease of the genitals or following prolonged suckling of the breast.

But, to our knowledge, the literature contains no reference to milk secretion following surgery of the thoracic cage. Since July, 1945, we have had ten such cases, the last one in June, 1948. The first one occurred following a primary anterior thoracoplasty. Nine cases followed a thoracoplasty and one case followed a pneumonectomy. Undoubtedly other such cases have occurred but have not been detected.

OPERATIVE TECHNIQUE

Because the operations are a primary factor in the production of lactation in this group, they will be described in brief. Four cases followed a first-stage posterior thoracoplasty, two cases followed a second-stage posterior thoracoplasty, three cases followed a first-stage anterior thoracoplasty, and one case followed a pneumonectomy.

In the first-stage posterior thoracoplasty, a long periscapular incision is made and the bony thorax reached by section of the latissimus dorsi, trapezius, and rhomboideus muscles. The origins of the serratus magnus muscle are separated from the upper five or six ribs and the scapula and the anterior chest wall are then retracted. The third and second ribs are removed subperiosteally up to the cartilage and including the associated transverse vertebral processes. The first rib is similarly removed including its cartilage. The periosteal beds are then formalinized and the wound closed in layers without drainage. The breast itself is not traumatized directly although a varying degree of local trauma does occur to it and many of its nerve fibers from the intercostals are undoubtedly torn and injured. Some degree of submuscular serosanguineous fluid always develops and may need occasional aspiration.

In the second-stage posterior thoracoplasty (done about twenty-one days after the first stage) the bony chest cage is reached through the lower part of the scar resulting from the first operation. The fourth and fifth ribs are re-

From the Hopemont Sanitarium, Hopemont, W. Va., and the West Virginia University School of Medicine, Morgantown, W. Va.

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*Present address: Veterans Administration Hospital, San Fernando, Calif.

moved subperiosteally up to the cartilages and the associated transverse vertebral processes are resected. The periosteal beds are formalinized and the wound closed in layers without drainage. A moderate degree of serosanguineous drainage occurs in the first several days postoperatively.

In the first-stage anterior thoracoplasty a perimammary incision is made. The bony chest cage is exposed by retracting the breast and pectoralis major muscle, and by freeing the origins of the pectoralis minor muscle from the ribs. Then long segments of ribs one, two, three, and four are removed subperiosteally to about the posterior axillary line. The cartilage of the first rib only is removed. The periosteal beds are then formalinized and the wound closed in layers without drainage. In these cases, the evidences of local trauma to the breast and skin are greater than in the posterior operation and there is usually a moderate amount of subpectoral serosanguineous exudate.

In the pneumonectomy patient a relatively short periscapular incision was made from the level of the fourth rib posteriorly around the scapula, and the sixth rib was removed subperiosteally. The pleural cavity was entered through the periosteal bed and the lung was removed. The wound was then closed in layers without drainage. There resulted a moderate degree of local trauma about the breast and the line of incision.

CASE REPORTS

CASE 1.—E. G., No. 11454, was a white woman, 41 years of age. She had far-advanced pulmonary tuberculosis predominantly on the left side with extensive cavities extending from ribs two to eight posteriorly. The first thoracoplasty stage was done through an anterolateral incision under cyclopropane-oxygen anesthesia on July 27, 1945; long anterior segments of the upper four ribs were removed subperiosteally. The second stage was done through the usual posterior approach Aug. 30, 1945, under cyclopropane and the posterior segments of the upper five ribs were removed. Two more stages were done later with a total removal of ten ribs and closure of the cavities.

The patient's menstrual periods began at 16 years of age, and occurred regularly every 28 days, lasting for five days. She had borne two children and had a considerable amount of breast milk each time. The breasts had now been dry for years. At the time of operation the patient was well nourished, plump, and had normal well-developed breasts. Her height was 65 inches, weight 151 pounds. Pelvic examination revealed no abnormalities.

She had a normal period from July 1 to 5. The first thoracoplasty was done July 27. She began to menstruate July 28. Three days later (July 31) her breasts became full and, on palpation, several cubic centimeters of creamy white free-flowing milk could be expressed from both breasts, predominantly the left. The subsequent menses and operations did not affect the lactation which continued for about six months. After two months the milk decreased in amount and the breasts became dry in January, 1946.

CASE 2.—M. P., No. 11308, a 34-year-old white woman, had far-advanced bilateral tuberculosis predominantly on the left side with an 8 cm. cavity extending from ribs three to seven posteriorly. The first thoracoplasty was an anterior stage done Nov. 15, 1945, under cyclopropane-oxygen anesthesia; the anterior segments of the upper four ribs were removed subperiosteally. The second stage was done Jan. 4, 1946, through a posterior approach, and a third stage Jan. 24, 1946. A total of seven ribs was removed with resulting cavity closure.

The patient began to menstruate at 11 years of age, and had a fairly regular 28-day cycle, with periods lasting 5 days. She has had three children, 15, 11, and 2 years of age. All were breast fed for thirteen months and she had abundant milk. After cessation of breast feeding the breasts became completely dry in several weeks. At the time of operation she

was well nourished, short and stocky (height 63 inches, weight 143 pounds), and had well-developed normal breasts. Pelvic examination showed normal findings.

The patient had a normal menstrual period November 8 to 12. On November 15 the anterior thoracoplasty was done. Immediately afterward the left breast became enlarged and three days postoperatively she noted a fullness and soreness which she attributed to the operation. On November 20 about 400 c.c. of serosanguineous fluid were removed from the subpectoral space but the breast remained full and sore. On November 29, the patient awaking from sleep in pronation noted a large wet spot on her gown opposite the left breast. Palpation resulted in the expression of thick, creamy milk from both breasts but predominantly from the left. One could collect 10 to 20 c.c. from the left breast at any one time in a steady stream and about one-half as much from the right. She then felt (in retrospect) that she had probably had milk in her breast on the third postoperative day and was sure she could have expressed it had she realized milk was present. She also stated that her left breast felt as though it contained about one-half the amount of milk she had had when she nursed her babies. The lactation was unaffected by the next two operations or the subsequent menses. The breasts continued to have considerable milk for about eight months, then showed a gradual decrease. The left breast finally became dry twenty-seven months after the start of lactation and the right one after twenty-two months.

CASE 3.—F. C., No. 12175, a Negro woman, 32 years of age, had far advanced pulmonary tuberculosis predominantly on the left side with a 6 cm. cavity under ribs three to six posteriorly. The first thoracoplasty was done through the posterior approach on Dec. 11, 1945, under cyclopropane-oxygen-ether anesthesia and the upper three ribs were removed subperiosteally. The second stage was done Jan. 26, 1946, under nitrous oxide-oxygen-ether anesthesia. A third stage was done three weeks later and a total of eight ribs was removed.

Her menses began at 13 years of age and occurred in a regular 28-day cycle, lasting 5 days. She had been pregnant four times but miscarried each time in the fifth month. At no time did she have milk in her breasts, which were normal and well developed. Pelvic examination revealed no abnormalities.

The first thoracoplasty was done December 11, and the next day she began to have a normal period. Three days later (December 15) both breasts became full, especially the left one, and milk could be easily expressed from both. About 10 c.c. of thick creamy-white milk could be expressed from the left side at any one time and about 5 c.c. from the right side. Pressure forced the milk out in a stream. The menstrual period ended December 17. The next two operations had no effect on the lactation and the subsequent menses were normal. Both breasts continued to secrete milk freely for six months, then lessened gradually, and dried in twelve months.

CASE 4.—L. J., No. 12125, a white woman, aged 32 years, had far-advanced pulmonary tuberculosis predominantly on the right side with a 4 cm. cavity under ribs four, five, and six posteriorly. A right-sided thoracoplasty was planned. The first stage was done Jan. 17, 1947, through the posterior approach under Pentothal Sodium intravenously, followed by nitrous oxide, oxygen, and ether. Ribs one and two were completely removed and only the posterior half of the third. The second and third stages were done Feb. 7, 1947, and May 2, 1947, under similar anesthesia. A total of eight ribs was removed and the cavity closed.

The patient's menses began at sixteen years and were irregular until after the first pregnancy. The cycle was 30 days, the periods lasting 4 days. She had two children, aged 13 years and 11 years. She had a considerable amount of milk both times although she breast fed the first child only for three months. Her breasts had been dry for more than ten years. At the time of the operation she was well nourished and of normal build (height 67 inches, weight 120 pounds). The breasts were normal and pelvic examination showed normal findings.

Her menstrual period began January 12 and ended January 16. The first thoracoplasty was done January 17 and on January 19 the breasts became full and sore, and milk could be expressed. About 5 to 10 c.c. of creamy white milk could be easily expressed from the

left breast (opposite to the side operated upon) and about 3 to 5 c.c. from the right one. The subsequent operations and menses had no effect upon the lactation although both the second and third stages were done one day prior to her menses. In August, 1947 (seven months later), only 4 c.c. thin yellowish milk could be expressed from the left breast and 2 c.c. thick creamy milk from the right one. The quantity lessened gradually and in December, 1947, both breasts became dry after lactating for eleven months.

CASE 5.—E. H., No. 12572, a 28-year-old white woman, had far-advanced pulmonary tuberculosis predominantly on the left side with a 4 cm. cavity under ribs three to five posteriorly. A left thoracoplasty was done. The first stage was performed March 21, 1947, through the posterior route under cyclopropane-oxygen-ether anesthesia. Two more stages were done later. A total of seven ribs was removed and the cavity closed.

The patient's menses varied from 25 to 30 days and lasted 4 days. She had one child, aged 4 years, who had been bottle fed although the patient had considerable breast milk. The breasts dried completely in six weeks. The patient was tall and slender (height 67 inches, weight 117 pounds) but had well-developed breasts. Pelvic examination showed normal findings.

The first thoracoplasty was done March 21; on March 23 her period began, and on March 25 milk was expressed from her breasts. She felt that the next two operations increased the fullness in both breasts slightly. The next period began April 29 and the one following on July 14. For the first week there was more milk in the left side, then the right one presented more and continued to do so. One could express 5 to 15 c.c. of creamy milk from each breast easily, and they would often drain spontaneously. In August the milk lessened in amount and in December, 1947, both breasts became dry after a lactation period of nine months.

CASE 6.—E. C., No. 12699, a 31-year-old Negro woman, had far-advanced pulmonary tuberculosis predominantly on the left side with a 7 cm. cavity under ribs three to six posteriorly. A first-stage left thoracoplasty was done by the anterior route May 24, 1947, under Pentothal Sodium, nitrous oxide-oxygen-ether, and the anterior segments of the upper four ribs were removed. The second stage was a posterior one and was done June 20, 1947, under cyclopropane. The third stage was done July 11, 1947, under nitrous oxide. A total of eight ribs was removed and the cavity closed.

The patient's menses began at 16 years and were very irregular for the first six years but then became regulated in a 28-day cycle, lasting 5 days. She had been pregnant twice, at ages 18 and 27 years, but aborted both times at three months. There was no lactation. At the time of her operation she was 60 inches tall and weighed 112 pounds. She was short and stocky and had normal well-developed breasts. Pelvic examination was normal.

She began to menstruate May 17 and the period ended May 24. The first thoracoplasty was done May 24. The next day the left anterior thoracic wall became swollen due to the operative trauma and subpectoral fluid. On May 27, the enlarged left breast became sore, and milk could be expressed. There was no milk in the right breast. The next two operations and menses had no effect on the lactation. One could express from 5 to 10 c.c. milk at any one time from the left breast. The right one was dry at all times. She continued to secrete milk until January, 1948, a period of seven months.

CASE 7.—L. D., No. 12698, a Negro woman, 22 years old, had far-advanced pulmonary tuberculosis predominantly on the left side with a 4 cm. cavity under ribs four to six posteriorly. A first-stage posterior thoracoplasty was done May 23, 1947, under Pentothal Sodium, nitrous oxide-oxygen-ether anesthesia with removal of the upper three ribs. The second stage was done June 20, 1947, under cyclopropane-oxygen-ether anesthesia with removal of ribs four and five. The third stage was done July 11, 1947, under Pentothal Sodium, nitrous oxide-oxygen-ether anesthesia with removal of ribs six, seven, and eight. The cavity then closed.

The patient's menses began at 14 years of age, recurring at intervals of 25 to 35 days, and lasting 6 or 7 days. She was not married but admitted having had sexual contact since

the age of 17 years; however, she denied ever having been pregnant or having missed a period. She had never noted any secretion in the breasts. She was 65 inches tall and weighed 115 pounds. The breasts were nulliparous and well developed. The pelvic organs were normal on examination.

She had a normal period from May 4 to 10. The first-stage thoracoplasty was done May 23. No lactation occurred. The second-stage thoracoplasty was performed June 20, her period began June 22, and the next day both breasts became full and sore, and one could express several drops of milk from each breast. The period ended June 29. The next operation done July 11 produced no effect on the lactation. The next period occurred July 15 to 22.

Both breasts showed an equal amount of milk. One could express about 5 to 8 c.c. of freely flowing creamy milk during one or two minutes. Once, while she was lying face downward, some milk ran out spontaneously on the sheet from the right breast. In September, 1947, one could express only several thick drops of creamy milk from each breast. In January, 1948, both breasts became dry, after a period of seven months.

CASE 8.—B. P., No. 12724, a 22-year-old Negro woman, had far-advanced pulmonary tuberculosis, predominantly on the right side with two cavities measuring 3 cm. to 4 cm. under ribs four to seven posteriorly. A first-stage posterior thoracoplasty was done June 20, 1947, under cyclopropane-oxygen-ether anesthesia with removal of the upper three ribs. A second and a third stage were done July 11, 1947, and Aug. 8, 1947, under Pentothal Sodium, nitrous oxide-oxygen-ether anesthesia. A total of eight ribs was removed and the cavities closed.

The patient's menses began at 11 years of age with a 28-day cycle, lasting 5 days. The patient was single and denied ever having had sexual contact. She was of moderate build and height, and showed well-developed normal virginal breasts. A pelvic examination was not done but a rectal examination showed normal findings.

She had a normal period May 24 to 29. The first thoracoplasty was done June 20. A normal menstrual period started June 21, the breasts became tender June 22, and milk could be expressed from both breasts June 23. The menstrual period ended June 26. The second thoracoplasty was done July 11, and the menses occurred July 24 to 29. The third operation was done August 8 and the following period occurred August 23 to 28. The second and third operations and the following menses had no effect on the lactation.

The second day following the operation of June 20, the left breast became very tender but was normal in size. The right breast on the side operated upon was swollen due to some subpectoral fluid and operative trauma. The next day one could express several drops of milk from both breasts on several occasions. The milk was creamy and thick but was freely flowing. The right breast contained more milk than the left. Following the third operation the milk decreased in amount and, at that time, the right breast yielded several drops of thick milk and the left breast two or three drops of thin milk. By Sept. 18, 1947, both breasts were dry, after a period of three months.

CASE 9.—P. P., No. 12700, a 26-year-old Negro woman, had a far-advanced pulmonary tuberculosis. The left side was clear but the right side showed extensive disease throughout and a 4 cm. lower-lobe cavity under ribs seven to nine posteriorly. She was considered a favorable case for pulmonary resection. A right pneumonectomy was done May 23, 1947, under Pentothal Sodium, nitrous oxide-oxygen-ether anesthesia. A posterior periscapular incision was made extending to the anterior axillary line, the muscles were freed, and the sixth rib was removed subperiosteally; the pleural cavity was entered and the lung removed. This was followed later by a two-stage thoracoplasty.

The patient's menses began at 13 years of age, recurred every 28 to 35 days, and lasted about 3 days. She was married at 19 years of age and had had three pregnancies. Following the first two pregnancies she had only a small amount of milk for several weeks but following the third, which resulted in a miscarriage and fetal death in 1944, she had a considerable amount of milk. However, the breasts dried in several weeks. She was 62 inches tall and weighed 103 pounds. The breasts were small but normal. Pelvic examination presented normal findings.

She had a normal period April 26 to 29. The right pneumonectomy was done May 23, the menstrual period began May 24, the left breast became sore and full on May 26. Unfortunately it was not palpated for secretions. The period ended May 27. Another period began on July 1 and ended on July 4, and on this date the left breast again became sore and full and, on palpation, yielded about 3 c.c. creamy white milk. The right breast (the side operated upon) was dry. The patient states that (in retrospect) she was sure that she had had milk in the left breast on May 26, three days postoperatively, because it was sore and tender and felt "full." The subsequent thoracoplasty operations and menses did not affect the lactation. One could express 2 to 5 c.c. milk from the left breast several times daily but none from the right one. Milk was present until January, 1948, a period of about seven months.

CASE 10.—M. L., No. 12878, a white woman, aged 44 years, had far-advanced pulmonary tuberculosis with a 4 cm. cavity under ribs three to five posteriorly on the right side. A first-stage posterior thoracoplasty was done May 6, 1948, under Pentothal Sodium, cyclopropane-oxygen-ether, and the first, second, and posterior half of the third ribs were removed. The second stage was done May 28 with removal of the anterior half of the third rib and the entire fourth and fifth ribs. The third stage was done June 21 with removal of ribs six and seven. The cavity then closed. The anesthesia for the second and third stages was similar to that used during the first operation.

The patient's menses began at 16 years and had been of a regular type, every 28 days, lasting 5 days. In the last 4 years, however, they had been irregular and would occur anywhere from two to six weeks. She was married at 19 years and had had four pregnancies. Three were full term and one was an abortion at three months. One infant died in three weeks from "croup" but the other two did well and were nursed for 11 and 16 months, respectively. She had had an adequate supply of milk. Following weaning, the breasts dried in two months, and had been dry for ten years. Before her operation she was 67 inches tall and weighed 140 pounds. The breasts were normal and pelvic examination was normal. She stated that she had never had any soreness or fullness in the breasts prior to her menses.

She had one period from May 1 to 5. The first-stage thoracoplasty was done May 6. Daily palpation of the breast revealed no secretions. The next period began May 21 and ended May 25. The second thoracoplasty was done May 28 and on June 1 palpation revealed milk in both breasts. The third operation was done June 21 and she began to menstruate June 22 but the lactation was not affected. The patient had no fullness or tenderness of the breasts at any time. However, palpation yielded white creamy milk—about 4 to 8 c.c. from the right breast daily and about 3 to 5 c.c. from the left. At the present time (Sept. 1, 1948) the patient still yields similar amounts daily.

SUMMARY OF CASE REPORTS

The ten patients varied from 22 to 44 years of age and represented a normal cross section of height, weight, and body build. The breasts in all were well developed and showed no abnormalities. The other sex characteristics were normal. Apart from tuberculosis they had no systemic disturbances with the exception of one patient who had had syphilis and had been treated successfully. Five patients were white and five Negro, giving a relatively high percentage of Negro patients, since they formed only about 10 per cent of our thoracoplasty cases. Eight patients had been pregnant and only one denied sex contact. Their lactation history was normal as a group.

The amount of milk varied from several drops to 15 c.c. expressed at any time, and the daily production varied from 5 to 25 c.c. In all cases, the secretion showed the color, consistency, and taste of milk or creamy milk. In three patients, the milk flowed spontaneously on several occasions. The color

and creaminess varied from one patient to another and from one time to another in the same patient. It showed an occasional variation in the two breasts. In five of the patients, milk secretion would not have been detected if proper palpation of the breast had not been done or if there had been no pressure on the breasts.

Table I summarizes the features of the lactation with respect to the amount of milk produced by each breast and the duration of the lactation. One patient had bilateral and equal milk secretion; five patients secreted more milk from the breast on the side operated upon; two patients secreted more milk from the side not operated upon; one only on the side operated upon; and the pneumonectomy patient only from the side not operated upon. The duration of secretion varied from three to twenty-seven months, with an average of about ten months.

Unfortunately, a sufficient number of detailed milk analyses were not made. The secretion had a milky or creamy taste and "soured" on standing for a day. Numerous fat globules were present microscopically and by stain. Analysis of the pooled sample done by the late Dr. P. L. MacLachlan of the Biochemistry Department showed the presence of protein, lactic acid, and large amounts of fat containing unsaturated fatty acids. When soured and shaken with water a precipitate occurred which resembled butter, and which was highly soluble in chloroform and absorbed iodine. The milk of Patient M. L. (Case 10) showed 2.6 per cent butter fat, 4.96 per cent lactose, casein, and reducing sugar.

TABLE I. FEATURES OF THE LACTATION

CASE	1	2	3	4	5	6	7	8	9	10	TOTAL
White	x	x		x	x					x	5
Negro			x			x	x	x	x		5
Posterior thoracoplasty			x	x	x		x	x	Resection	x	7
Anterior thoracoplasty	x	x				x					3
Lactation after second stage							x			x	2
Side operated on	L	L	L	R	L	L	L	R	R	R	R4 L6
Bilateral and equal lactation							x				1
More milk on side operated upon	x	x	x					x		x	5
More milk on side not operated upon				x	x						2
Milk only on side operated upon						x					1
Milk only on side not operated upon									x		1
Approximate daily yield, c.c.	10	40	25	15	30	15	20	5	15	10	
Duration, months	6	27	12	11	9	7	7	3	7	–	

UNIMPORTANT FACTORS

The patients varied in height from 60 inches to 67 inches and in weight from 103 to 151 pounds; two patients were slender in build, four were of medium build, and four were of stocky build. The breasts in all were well developed and normal. None had other systemic diseases or extrapulmonary tuberculosis. The diet was regular and somewhat high in protein. The blood counts, blood type, Rh factor, and blood coagulation factors were not significant. The urinalyses were normal in all cases. Preoperative medication included barbiturates and Dilaudid. Seven patients had cyclopropane-oxygen-ether anesthesia and three had Pentothal Sodium intravenously, followed by nitrous oxide-oxygen-ether. During the operation, blood, saline, and glucose were given to all patients. Stimulants were used in only two cases and included Adrenalin, cortin, ephedrine, and Neosynephrin. Postoperatively, narcotics, sedatives, and penicillin were used. Early ambulation was practiced and the patients were encouraged to get out of bed one to three days postoperatively. The postoperative fever was within expected limits. The dressing appeared to have no pressure effects on the breasts.

IMPORTANT FACTORS

All patients were in the active menstrual age. The five Negro women formed an unusually high percentage as the great majority of the operations we have done have been on white women. The three anterior thoracoplasties also formed a relatively high number as this type of operation is done in less than 10 per cent of our thoracoplasty cases. Seven cases followed the first-stage thoracoplasty and two followed a second stage.

The extent of surgical trauma is undoubtedly great and is to be expected following the section and freeing of so many large muscles and the subperiosteal removal of the ribs. There is always some collection of serosanguineous fluid submuscularly. The skin may occasionally show evidence of bruising. The processes of repair go on for some months. The breast tissue is not directly traumatized and the indirect trauma (retraction) is not very great. Undoubtedly, there must be considerable trauma to the intercostal nerves and fine branches although no paresthesias or anesthesias were noted.

When all the possible etiological factors are reviewed, the three that are most prominent are the day of the operation, the date of the menstrual onset, and the date of lactation. Table II shows the relationships between them. In all cases, lactation followed the operation in two to four days—two days in one case, three days in five cases, and four days in four cases. In six cases the expected menses began one or two days after the operation. In four cases the menses occurred seven days, seven days, seven days, and five days prior to the operation and were completed three days, three days, two days, and one day prior to the operation. The last day of the period appeared to have no significance.

THEORETICAL CONSIDERATIONS

Since the menstrual cycle, lactation, and the operation are closely connected, the physiology pertaining to them will be reviewed briefly. There

is so much disagreement at present regarding the status and action of the hormones that only the more accepted views will be mentioned.[4, 5]

Following the onset of the menstrual period, the pituitary gonadotrophin acts first upon the ovarian follicle to produce estrogens and maturation of the ovum and later upon the corpus luteum to produce progesterone. The pituitary then becomes inactive due either to an innate rhythm or to an inhibition by the high estrogen level. This is followed by a rapid drop in the production of the ovarian hormones, and menstruation begins. During the premenstrual phase the breasts become enlarged and tender, and the ducts and alveoli proliferate and show some serous secretion. The estrogens develop the ducts and the progesterone the alveoli. When the menstrual period begins the breasts show regressive changes which continue for about a week. Although there is no mention of lactogenic hormone being formed during the cycle some recent experiments suggest that a lactogenic hormone may be necessary for the development of the corpus luteum.[4]

TABLE II. TIME RELATIONSHIPS BETWEEN THE DAY OF THE OPERATION (O), BEGINNING OF THE MENSTRUAL PERIOD (M), AND BEGINNING OF LACTATION (L)

CASE	1	3	8	9	5	7	2	6	4	10
Day 1	O	O	O	O	O	O	M	M	M	M
2	M	M	M	M						
3					M	M				
4			L	L		L				
5	L	L			L					
6									O	
7										
8							O	O	L	O
9										
10										
11							L	L		
12										L

When pregnancy occurs, the chorionic tissue produces gonadotrophin, estrogen, and progesterone. The last two hormones increase to a very high level, particularly in the terminal phase of pregnancy, and their production may reach a height of 20 to 50 times that seen maximally in the menstrual cycle. Following the removal of the placenta the hormones disappear within several days.

As a result of the stimulation of the mammary glands by the estrogen and progesterone during pregnancy, the ducts and alveoli show hyperplasia and hypertrophy and, toward the end of pregnancy, become filled with a secretion resembling colostrum. True lactation appears three to four days following childbirth. It is believed that the drop in the estrogen level following childbirth stimulates the pituitary to produce lactogenic hormone. The lactogen then initiates lactation in a properly prepared breast. Once started, the continuation of lactation is maintained by the mechanical act of suckling which stimulates the pituitary through the nerve pathways and causes further production of the lactogenic complex of hormones.

It is to be noted that the curves for gonadotrophin, estrogens, and progesterone have many similarities during the menstrual cycle and during pregnancy, although the former are on a much lower level. The role of lactogen in the menstrual cycle is not clear.

As mentioned, postpuerperal lactation is initiated by the lactogenic hormone in a breast properly prepared and developed by estrone and progesterone; it is maintained by the further production of lactogenic hormones as a result of stimulating the pituitary by the neurogenic mechanical act of suckling. One may conjecture that if the breast tissue were adequately prepared and if the neurogenic stimulus were sufficiently powerful, lactation might occur even during the menstrual cycle. Such an adequate preparation of the breasts may result from either an unusually high estrogen-progesterone level, a breast tissue unusually sensitive to normal levels, or both factors. The lactogenic hormone factor may be present normally during the menstrual cycle and be enhanced by the neurogenic stimulus, or a powerful neurogenic stimulus may in itself cause the pituitary to produce the hormone.

In this group of ten cases, no hormonal assays were made and we do not know whether these patients had a high estrogen-progesterone level or whether the breast tissue was unusually sensitive to normal levels of the hormones or whether both factors were present. The neurogenic stimulus to lactation was presumably supplied by the operation with its attendant stimulation of the nerve endings in the breast. The glandular elements are supplied by the fourth, fifth, and sixth intercostals and the accompanying sympathetic fibers; the skin is supplied by the anterior and lateral cutaneous branches of the second to the fifth intercostals and the supraclavicular branches of the cervical plexus. The maintenance of lactation for some months may be explained by the continued mechanical stimulation of the nerves by the processes of repair.

Since only the hormones usually present in the menstrual cycle are involved and since the operation (neurogenic factor) resulted in milk secretion, it is highly probable that lactogenic hormone may be present normally during the menses. Ordinarily, the lack of lactation during normal menses may be due to the small amount of lactogen, the lack of adequate preparation of the breast tissue, or both.

On the basis of this theory the secondary factors of significance will be explained. The high proportion of Negro women suggests that they have either a higher hormonal level or a more sensitive breast tissue, or both. The occurrence of lactation among both parous and nulliparous women and even in a virgin shows that no hormones other than those occurring normally in the menstrual cycle probably take part in the production of lactation. The high proportion of anterior thoracoplasties in this series is due probably to the fact that the damaged nerve fibers of the breast are more intensely stimulated in them than in the posterior operations. Seven out of the nine thoracoplasty patients lactated following the first stage at which not only the first, second, and third ribs were removed but in which the serratus magnus origins were

separated from the upper five ribs, thus disrupting many of the nerve fibers to the breast. In two patients the first thoracoplasty operation did not produce sufficient neurogenic stimuli but the subsequent second stage apparently added enough stimuli to cause lactogenic production and secretion of milk. The low incidence of lactation in pneumonectomies is due probably to the fact that the nerve fibers to the mammary glands are only little disturbed either directly by the operation or indirectly later by the exudative and reparative processes. It is more difficult to explain the exact mechanism which occurred in Cases 2, 4, 6, and 10 in which the menses began and ended prior to the operation. It is possible that in them the level of ovarian hormones was still high during the menstrual period and dropped just before the operation.

This theory may also explain some of the abnormal causes of lactation mentioned in the first paragraph in which the neurogenic factor is represented by such trauma as titillation and a burn.

SUMMARY

1. Ten cases of lactation are described in nonpuerperal women following thoracic operations. Nine followed extrapleural thoracoplasty and one followed a pneumonectomy.

2. It is believed that the explanation of the lactation lies in the same hormonal factors present during the normal menstrual cycle, pregnancy, and lactation.

3. The lactogenic hormone factor usually resulting from the mechanical stimulation of the nerve fibers of the breast by the act of suckling was supplied, in these cases, by the operation.

4. It is possible that lactogenic hormone may be present normally during the menstrual cycle.

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